DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

P940001

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Date: SEP 12 1997

From: Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health(CDRH)

Subject: Premarket Approval of Gensia, Inc.
GenESA System

To: The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:
(1) a premarket approval order for the above referenced medical devices (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the devices (Tab C)

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Hung Trinh, CDRH, HFZ-480, September 9, 1997, 594-1287

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DRAFT

P940001

Food and Drug Administration

[DOCKET NO. _____]

Gensia, Inc.; Premarket Approval of GenESA® System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Gensia, Inc., San Diego, CA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the GenESA® System. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of September 12, 1997, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and DrugAdministration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Mr. Hung Trinh,

Center for Devices and Radiological Health (HFZ-480),

Food and Drug Administration,

9200 Corporate Blvd.,

Rockville, MD 20850,

301-594-1287.

SUPPLEMENTARY INFORMATION: On January 3, 1994, Gensia, Inc., San Diego, CA 92121, submitted to CDRH an application for premarket approval of the GenESA® System. The device is an infusion pump and is indicated for the following indication:

The GenESA® System delivers arbutamine, a catecholamine, through a closed-loop, computer-controlled drug-delivery system to elicit acute cardiovascular responses similar to those produced by exercise. In patients with suspected coronary artery disease (CAD) who cannot exercise adequately, stress induction with the GenESA® System is indicated as an aid in diagnosing the presence or absence of CAD.

The effectiveness of the GenESA® System has been demonstrated in clinical studies using radionuclide myocardial perfusion imaging to predict the results of coronary angiography. These studies were in patients with high and lower risks of CAD and utilized blinded, central reading of images. Estimates of sensitivity, specificity and predictive values are presented in the "Clinical Trials" section.

Although the effectiveness of the GenESA® System was also assessed in similar clinical studies utilizing echocardiography to predict the results of coronary angiography, the blinded, central reading of the images from the lower-risk echocardiography study was technically inadequate. Estimates of sensitivity, specificity and predictive values, based on the non-blinded readings of echocardiograms at the local study sites, are presented for the lower-risk patients (see the Clinical Trials section of

the GenESA® (arbutamine) Package Insert). For the study of high-risk patients, the estimates are based on valid, blinded, central reading of images. Like exercise testing, cardiac stress testing with the GenESA® System must always be performed under the direct supervision of a physician, and cardiac emergency equipment and supplies (defibrillator, intravenous b-blocker, etc.) must always be available. Arbutamine must not be administered without use of the GenESA® Device.

In accordance with the provisions of section 515(c)(2) of the act (21 U.S.C. 360e(c)(2)) as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General Hospital and Personal Use Devices panel of the Medical Devices Advisory Committee, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On September 12, 1997, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity for Administrative Review

Section 515(d)(3) of the act authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under 21 CFR part 12 of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 21 CFR 10.33(b). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in

brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 1 2 1997

Ms. Cynthia Luchetti
Director, Regulatory Affairs
Gensia, Incorporated
9360 Towne Center Drive
San Diego, California 92121

Re: P940001
GenESA® System
Filed: January 3, 1994
Amended: August 15, 1994, March 10, 1995, May 15, and 22, 1995, October 2, 1995, September 12, 1996, November 12, 1996, May 20, 1997, September 9, 1997

Dear Ms. Luchetti:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the GenESA System. This device is indicated for the following indication:

> The GenESA® System delivers arbutamine, a catecholamine, through a closed-loop, computer-controlled drug-delivery system to elicit acute cardiovascular responses similar to those produced by exercise. In patients with suspected coronary artery disease (CAD) who cannot exercise adequately, stress induction with the GenESA® System is indicated as an aid in diagnosing the presence or absence of CAD.
>
> The effectiveness of the GenESA® System has been demonstrated in clinical studies using radionuclide myocardial perfusion imaging to predict the results of coronary angiography. These studies were in patients with high and lower risks of CAD and utilized blinded, central reading of images. Estimates of sensitivity, specificity and predictive values are presented in the "Clinical Trials" section.
>
> Although the effectiveness of the GenESA® System was also assessed in similar clinical studies utilizing echocardiography to predict the results of coronary angiography, the blinded, central reading of the images from the lower-risk echocardiography study

was technically inadequate. Estimates of sensitivity, specificity and predictive values, based on the non-blinded readings of echocardiograms at the local study sites, are presented for the lower-risk patients (see the Clinical Trials section of the GenESA® (arbutamine) Package Insert). For the study of high-risk patients, the estimates are based on valid, blinded, central reading of images.

Like exercise testing, cardiac stress testing with the GenESA® System must always be performed under the direct supervision of a physician, and cardiac emergency equipment and supplies (defibrillator, intravenous b-blocker, etc.) must always be available. Arbutamine must not be administered without use of the GenESA® Device.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. FDA has designated your device for tracking.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have any questions concerning this approval order, please contact Mr. Hung Trinh at (301) 594-1287.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 5-2-95

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified

and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known

to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action

by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name:	Closed-Loop Infusion System
Device Trade Name:	GenESA® Device (The GenESA® Device is a component of the GenESA® System, comprising the drug GenESA® (arbutamine hydrochloride) and the GenESA® Device(dedicated closed loop infusion device))
Applicant's Name and Address:	Gensia, Inc. 9360 Towne Centre Drive San Diego, CA 92121
Date of Panel Recommendations:	none
PMA Number:	P940001
Date of GMP Inspection:	November 6, 1995
Date of Notice of Approval to the Applicant	SEP 12 1997

II. INDICATIONS FOR USE

The GenESA® System delivers arbutamine, a catecholamine, through a closed-loop, computer-controlled drug-delivery system to elicit acute cardiovascular responses similar to those produced by exercise. In patients with suspected coronary artery disease (CAD) who cannot exercise adequately, stress induction with the GenESA® System is indicated as an aid in diagnosing the presence or absence of CAD.

The effectiveness of the GenESA® System has been demonstrated in clinical studies using radionuclide myocardial perfusion imaging to predict the results of coronary angiography. These studies were in patients with high and lower risks of CAD and utilized blinded, central reading of images. Estimates of sensitivity, specificity and predictive values are presented in the "Clinical Trials" section.

Although the effectiveness of the GenESA® System was also assessed in similar clinical studies utilizing echocardiography to predict the results of coronary angiography, the blinded, central reading of the images from the lower-risk echocardiography study was technically inadequate. Estimates of sensitivity, specificity and predictive values, based on the non-blinded readings of echocardiograms at the local study sites, are presented for the lower-risk patients (see the Clinical Trials section of the GenESA® (arbutamine) Package Insert). For the study of high-risk patients, the estimates are based on valid, blinded, central reading of images.

Like exercise testing, cardiac stress testing with the GenESA® System must always be

performed under the direct supervision of a physician, and cardiac emergency equipment and supplies (defibrillator, intravenous b-blocker, etc.) must always be available. Arbutamine must not be administered without use of the GenESA® Device.

III. CONTRAINDICATIONS

Arbutamine is contraindicated in patients with idiopathic hypertrophic subaortic stenosis, in patients with a history of recurrent sustained ventricular tachycardia, in patients with congestive heart failure (NYHA Class III or IV), and in patients who have shown previous manifestations of hypersensitivity to arbutamine. The GenESA® System must not be used in the presence of an implanted cardiac pacemaker or automated cardioverter/defibrillator.

IV. WARNINGS

The GenESA® System is a combination product, comprising of the drug GenESA® (arbutamine) and the dedicated close loop device, the GenESA® Device. Following are the more significant warnings which apply to the GenESA® System. Please refer to section 1 of the device Directions for Use Manual for the complete list of warnings pertinent to the device and the instructions in the Package Insert for GenESA®(Arbutamine) for the complete list of warnings associated with use of the drug.

- Arbutamine is intended for use as a diagnostic agent ONLY.
- Arbutamine may precipitate or exacerbate supraventricular and ventricular arrhythmias and its administration is not recommended in patients with a history of sustained arrhythmias of this nature.
- Arbutamine should NOT be administered to patients receiving antiarrhythmic drugs, particularly Class 1 agents such as quinidine, lidocaine and flecainide.
- Arbutamine may cause rapid increases or paradoxical decreases in HR and systolic blood pressure. Discontinuation of arbutamine infusion results in reversal of these effects.
- The administration of arbutamine is not recommended in patients with recent (within 30 days) myocardial infarction, unstable angina, mechanical left ventricular outflow obstruction such as severe valvular aortic stenosis, uncontrolled systemic hypertension, a cardiac transplant, a history of cerebrovascular accident or peripheral vascular disorder resulting in cerebral or aortic aneurysm.
- Arbutamine is NOT recommended in patients with narrow angle glaucoma or uncontrolled hyperthyroidism.
- Arbutamine should NOT be administered to patients receiving digoxin, atropine (or other anticholinergic drugs) or tricyclic antidepressants. The use of atropine to enhance the chronotropic response to arbutamine is not recommended.
- Arbutamine, like other catecholamines, can produce a transient reduction in serum potassium concentration, rarely to hypokalemic levels.
- Beta-adrenergic antagonists may attenuate the response to arbutamine and should be withdrawn at least 48 hours before conducting a GenESA® Test.

- Arbutamine may cause a rapid elevation of HR and cardiac contractility. Therefore, continuous monitoring of HR and frequent determinations of blood pressure are MANDATORY.

- There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, arbutamine should be used during pregnancy only if clearly needed.

- Safety and effectiveness in children have not been established. Arbutamine is not recommended for use in persons under the age of 18 years.

VI. PRECAUTIONS

A listing of all precautions to be taken for safe use of the GenESA® Device are also listed in section 1 of the Directions For Use Manual. These include procedures to assure accuracy of ECG information, for operation on battery power and for maintenance of the device. Please also refer to the precautions listed in the drug instructions found in the Package Insert for GenESA® (Arbutamine).

VII. GenESA® SYSTEM DESCRIPTION

The GenESA® System is a pharmacologic stress system developed for use with electrocardiography (ECG), echocardiography, and radionuclide imaging (RNI) for the diagnosis and evaluation of coronary artery disease. It is a combination product which includes a novel catecholamine, arbutamine, and a proprietary closed-loop, computer controlled drug-delivery device to provide an alternative to traditional exercise stress testing.

Exercise stress testing, utilizing a treadmill and interpretive ECG monitoring, is employed to evaluate patients with known or suspected CAD. However the utility of treadmill exercise is limited, and a large segment of the population cannot exercise due to physical limitations, or otherwise cannot adequately attain the heart rate which is necessary for diagnosis of CAD. The GenESA® System provides a means to elicit controlled pharmacological stress as an alternative to exercise stress testing. The GenESA® System does not, however, provide for diagnosis of CAD, and must be used in conjunction with diagnostic imaging modalities such as echocardiography or radionuclide perfusion imaging.

The GenESA® System uses an integrated "computerized closed-loop system" to deliver arbutamine and this concept is illustrated in **Figure 1**. The drug is delivered via intravenous administration. The "Drug Delivery Controls" of the device allow the operator to select a maximal HR limit (HR Target) and rate of HR rise (HR Slope), start and stop drug delivery, maintain a given HR (HOLD HR), as well as other desired functions. The GenESA® System administers a small amount of arbutamine, measures the patient response, calculates the difference between the desired and actual response, and makes a dosing decision to achieve the desired response. This process is repeated frequently (every 15 seconds) allowing for a smooth and controlled patient response to arbutamine. The device also has many safety and monitoring features designed to maximize patient safety. The device is only to be used under direct supervision of a physician in conjunction with monitoring equipment suitable for diagnosis and safety monitoring of the patient (e.g. diagnostic ECG equipment).

GenESA® Drug (Arbutamine Hydrochloride)

Arbutamine is a sympathomimetic that exhibits increased selectivity for b-adrenoceptors over a-adrenoceptors in functional assays. The b-agonist activity of arbutamine provides cardiac stress by increasing HR, cardiac contractility and systolic blood pressure. Some a-receptor activity is retained in vivo, such that the degree of hypotension observed for given chronotropic activity is less with arbutamine than isoproterenol, a specific b-agonist.

Arbutamine is used as a cardiac stress agent to provoke myocardial ischemia secondary to its cardiac effects. Arbutamine increases cardiac work through its positive chronotropic and inotropic actions, while also probably limiting regional subendocardial perfusion and hence tissue oxygenation.

GenESA® Device

The GenESA® Device is illustrated in **Figure 2**. The main components of the device include the single channel ECG (HR monitor) and non-invasive blood pressure (NIBP) monitor, the closed-loop algorithm (CLA) that controls drug delivery, and the intravenous (IV) infusion pump. The device also contains an integrated printer which provides a printout of test results.

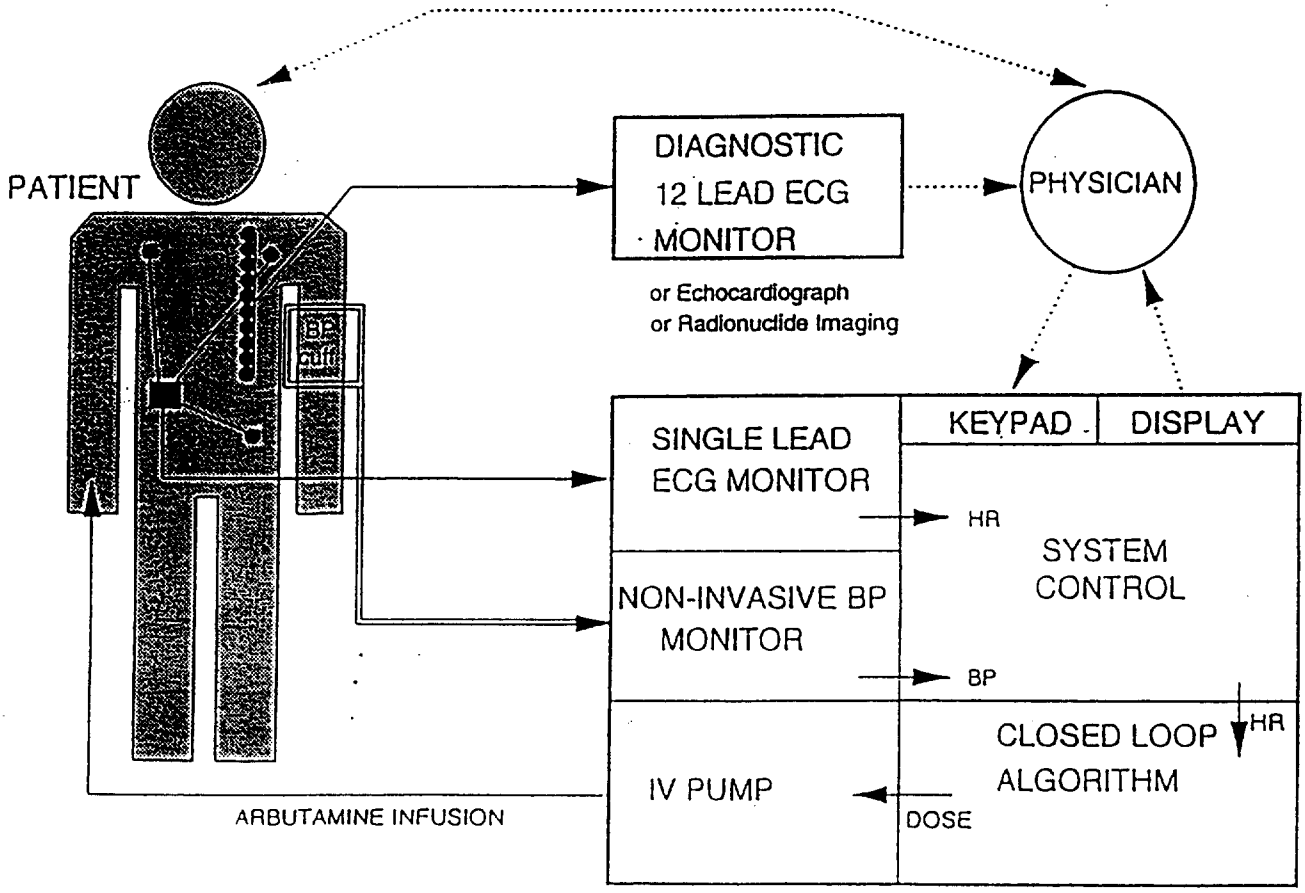


Figure 1 Schematic Representation of the GenESA® System

The single channel ECG and NIBP monitoring components are derived from a currently marketed medical device (the Propaq® series of monitors manufactured by Protocol

Systems, Inc.). The ECG monitor is used by the GenESA® Device to determine the patient's HR. The HR response and the physician selected HR Slope (rate of rise in HR) are the primary inputs from which the CLA determines infusion rate. A maximal HR limit (HR Target) is also selected before starting drug delivery, and represents an upper limit to facilitate the safe conduct of the test. The NIBP monitor is used for general patient monitoring but does not provide input to the CLA.

The IV pump is derived from a standard syringe pump, with minor modifications to accommodate only the arbutamine pre-filled syringe, provide occlusion detection, syringe-in-place detection, and syringe-near-empty detection. The IV pump is microprocessor based, and designed with redundant protection against over-pressure conditions and associated watchdog circuitry for microprocessor monitoring.

The CLA is a software program designed by Gensia to control the delivery of arbutamine to achieve a physician's preselected HR profile. The CLA controls the infusion rate based on the patient's weight (dosing is in mg/kg/min.), HR response, the physician selected HR profile and predetermined safety limits. The CLA first filters the monitored HR signal to eliminate artifacts and then smoothes the HR providing a good signal for feedback control. The GenESA® Device includes a "HOLD HR" feature that, when activated, allows HR to be maintained at approximately the existing level for up to five minutes.

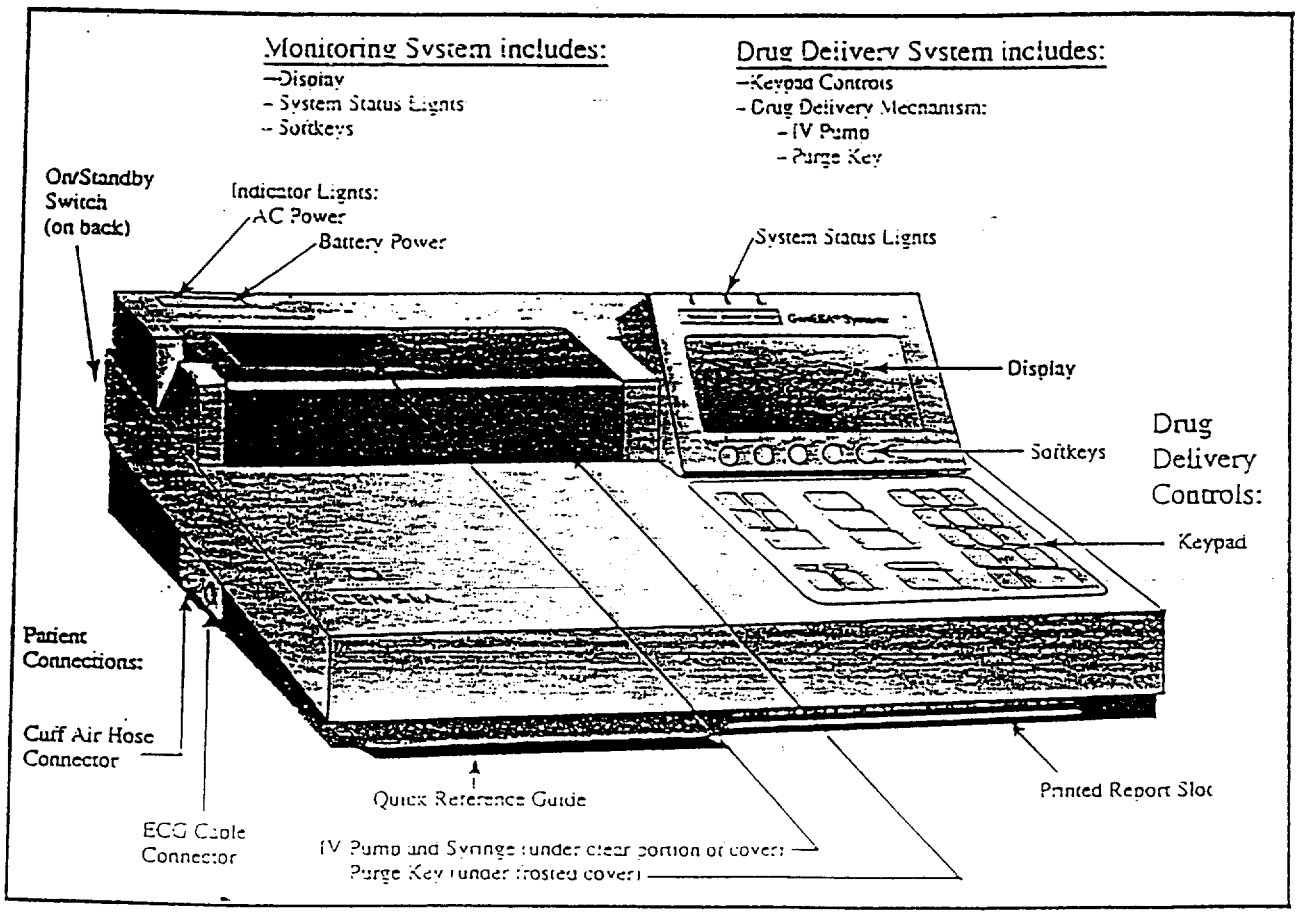


Figure 2. The GenESA® Device

Monitoring features of the GenESA® Device include the continuous display of ECG, HR, blood pressure and dosing information. In addition, the device has a series of "alerts" that warn of conditions that may require attention and "alarms" that stop drug delivery due to a potential safety hazard.

The GenESA® Device has been designed for use with industry standard NIBP and HR monitoring and infusion accessories. The Directions for Use specify the IV infusion sets, and ECG and NIBP accessories recommended for use with the device. The device has been designed and tested to meet the applicable sections of the AAMI Standards for ECG, NIBP and Infusion Devices, UL 544 Standard for Medical and Dental Equipment, CSA C22.2 No. 125-M Electromedical Equipment, and the IEC 601-1/-2 Electrical and Functional Safety Standards for Electromedical Apparatus.

The GenESA® System Test

Following appropriate preparation of the patient, the physician selects the desired HR Slope and HR Target. Upon starting the test, the GenESA® Device administers a small, standard dose of arbutamine and measures the patient's HR response. The device then calculates the difference between the desired and the actual HR response, and maintains or modifies, as necessary, the infusion rate. The maximum infusion rate delivered by the GenESA® Device is 0.8 ug/kg/min and the maximum total dose is 10 ug/kg. Reaching the preselected maximal HR limit (HR Target) is not an objective of the GenESA® test; the "HR Target" represents an upper HR boundary established to facilitate the safe conduct of GenESA® System tests. Other recognized endpoints of stress testing, such as intolerable symptoms or the presence of cardiac ischemia on ECG or echo, will often occur prior to reaching this maximal limit. In these circumstances the investigator will stop the arbutamine infusion. Prior to reaching the HR Target or other test endpoint, some patients may reach a maximum HR response to arbutamine referred to as HR saturation.

When the GenESA® Device detects no continued increase in HR (despite increasing infusion rates), a "Possible HR saturation, no increase in heart rate, increasing IV dose" alert will be triggered. If this condition persists, the alert will transition into an alarm and drug delivery will be interrupted. The alarm displayed depends upon the level of HR increase achieved. If the HR is 40 bpm or less above baseline then the message line will indicate "No increase in heart rate, increasing IV dose, restart if clinically appropriate" and restart is allowed. If the patient's HR is greater than 40 bpm over baseline, then the HR saturation alarm message will indicate "Heart rate saturation, do not restart, HR increase greater than 40 bpm" and restart is prevented by the device. In this case, the patient has reached a point on the dose-response curve where continued dosing with arbutamine is unlikely to elicit further increase in HR. Achieving HR saturation is an endpoint of a GenESA® System Test.

VII. ALTERNATIVE PRACTICES AND PROCEDURES

Role of Stress Testing in Clinical Practice

In clinical practice, the evaluation of patients with known or suspected CAD is performed sequentially to acquire as much diagnostic information as possible noninvasively and with the least risk, discomfort and financial burden to the patient. The evaluation begins with an assessment of risks and symptoms and, if warranted, progresses to the performance of noninvasive stress tests. The noninvasive stress test allows the clinician to confirm that the symptoms for which the patient seeks treatment occur in conjunction with objective evidence of myocardial ischemia. In patients suspected of having CAD, or

those with risk factors for CAD, producing ischemia by noninvasive stress testing may be the basis upon which other procedures, such as coronary angiography, are recommended. In patients known to have CAD, stress testing used with other adjunctive modalities, can evaluate the extent and severity of disease and its functional and prognostic significance.

Methods of non-invasive diagnostic testing should allow the physician to identify "high-risk" patients, for whom further investigation and/or treatment are appropriate. Conversely, it is at least equally important to identify those patients at "low-risk", for whom no further investigation is necessary, especially when the cost and the invasive nature of investigations such as coronary angiography are considered.

Methods of Diagnostic Testing

Angina pectoris is the most frequent clinical manifestation of CAD and is, in general, an exercise-induced phenomenon. Stress testing, usually with exercise, has therefore been used for many years to enhance the diagnostic utility of ECG, and, more recently, echocardiography and radionuclide myocardial perfusion imaging (RNI).

ECG is widely available, familiar to many clinicians and relatively inexpensive. Although relatively insensitive, exercise ECG is an appropriate initial diagnostic test in asymptomatic subjects at risk of CAD. The reported sensitivity (proportion of patients with angiographic CAD who have a positive stress test) of exercise ECG varies between 40-80%, with specificity (proportion of patients without angiographic CAD who have a negative stress test) ranging from 65-90%. Exercise ECG is also useful in the initial identification of patients at both low and high risk of CAD, in order to determine which patients require additional, and possibly invasive investigation. However, an abnormal resting ECG can preclude interpretation of the exercise test and therefore limit its utility.

Echocardiography has good sensitivity and specificity based on its ability to detect stress-induced wall-motion abnormalities, associated with functionally significant coronary artery lesions. The sensitivity and specificity of exercise echo has been reported to vary between 60-95%. In addition to its utility in the diagnosis of CAD, stress echo can have an important role in the assessment of prognosis, e.g., after myocardial infarction, particularly compared to ECG, and in identification of "viable" myocardium, potentially suitable for revascularization. The use of stress echo requires an appropriate level of expertise and training and can be limited by the difficulties in obtaining adequate echo images in some patients, particularly during exercise.

Radionuclide Perfusion Imaging, using thallium-201, has been shown to be useful in a variety of clinical applications. Sensitivity (ranging from 70-95%) and specificity (ranging from 65-90%) for the detection of CAD are good for both planar and single-photon emission computerized tomography (SPECT) imaging. SPECT imaging provides the potential for improved detection, localization and quantification of perfusion defects, as compared to planar imaging, due to the examination of thallium-201 distribution in sequential tomographic slices. Other imaging agents, such as technetium-99m sestamibi, are increasingly being used. Exercise RNI is able to stratify disease severity and assess prognosis, in patients with and without prior myocardial infarction. However, RNI imaging requires expensive equipment, highly trained personnel, and the administration of a radioisotope.

VIII. MARKETING HISTORY

European Marketing Authorization Application was filed with the EC Member States for GenESA® System on December 15, 1993. The following marketing approvals have since been received:

Sweden	December 19, 1994
United Kingdom	January 12, 1995
Luxembourg	February 3, 1995
Ireland	February 20, 1995
Germany	March 28, 1995
Netherlands	April 25, 1995
Denmark	May 30, 1995
Portugal	December 22, 1995
Belgium	March 14, 1996
Norway	December 9, 1996

IX. POTENTIAL ADVERSE EFFECTS OF THE SYSTEM ON HEALTH

Adverse events associated with use of the GenESA® System were recorded during controlled clinical trials (phase 3 and 3B) in 2082 patients with known or suspected CAD. The adverse events are predominantly related to the drug, arbutamine. The only adverse events reported as related solely to the GenESA® Device were single reports (0.05%) of hypoesthesia, paresthesia, and pain at the IV cannula site.

The most frequently reported adverse events in the 2082 patients were: tremor (15%), angina pectoris (12%), arrhythmias (12%), headache (9%), and hypotension (6%). Adverse events occurring in 31% of the 2082 patients are shown in the following table:

Table 3
Incidence of Most Frequent (≥1%) Adverse Events with Arbutamine

	Incidence (%) of Adverse Events
Tremor	15
Angina pectoris	12
Cardiac arrhythmias	12
Ventricular	6
Supraventricular	4
Headache	9
Hypotension	6
Chest pain	4
Dizziness	4
Dyspnea	4
Palpitation	4
Flushing	3
Hot flushes	3
Nausea	3

Paresthesia	2
Anxiety	1.9
Pain (non-specific)	1.8
Increased sweating	1.5
Fatigue	1.3
Taste perversion	1.3
Dry mouth	1.1
Hypoesthesia	1.0
Vasodilation	1.0

During clinical trials that included 2082 patients with known or suspected coronary artery disease, arbutamine administration was associated with 10 (<5%) **serious adverse events**, including 3 episodes of ventricular fibrillation, 1 episode of sustained ventricular tachycardia, 3 episodes of atrial fibrillation, 1 myocardial infarction and 2 cases of severe angina. Two of the three cases of ventricular fibrillation occurred after the GenESA® Device had detected a plateau in HR response and had terminated arbutamine infusion, but the physician restarted the infusion. There no deaths related to arbutamine.

X. SUMMARY OF STUDIES

Twenty six clinical studies have been performed with arbutamine. In Phase I clinical trials the safety of arbutamine in normal volunteers was investigated, primarily administering the drug "open-loop"(i.e.: with predefined infusion rates selected by the investigator). Initial parameters used to develop the CLA were collected. Phase I trials also evaluated the clinical pharmacology, pharmacokinetics and metabolism in man and investigated possible drug interactions. Phase 2 trials assessed the pharmacokinetic and pharmacodynamic profile of arbutamine and its preliminary safety and efficacy in patients with CAD.

In parallel with these early studies and the initial development of the CLA, the ESA (Exercise Simulating Agent) Research System was developed as an early forerunner of the GenESA® Device. The ESA Research System consisted of several individual devices (e.g. syringe pump, BP monitor, ECG monitor) which were interconnected with a personal computer. The system was used for the collection of physiological data and for the testing of the first four revisions of the CLA in Phase 1 and 2 Studies, 0111, 0115, 0117 and 0120 **(Refer to Table 4)**. The objective of these studies was to investigate the effects of intravenous administration of arbutamine, with delivery controlled by the CLA, primarily with respect to effects on HR and blood pressure, ability to induce cardiac ischemia, as well as evaluating the function of the device and CLA.

The ESA Clinical Device integrated all the functional elements of the system (IV pump, HR and BP monitor, microprocessors) into one device, except for the printer. The multinational Phase 3 clinical program began in April 1992 and involved a total of 697 patients **(Refer to Table 4)**. The objective of Phase 3 multicenter studies 0122, 0123, 0127, 0128 and 0129 was to evaluate the safety and efficacy of the ESA Device with respect to:

Table 4
Summary of Closed Loop Clinical Studies

Clinical Study No.	Summary of Study Objectives	Phase of Clinical Study	No. Enrolled	No. With Device Data	System	Revision of Algorithm
0111	Achievement of set HR in male volunteers	I	8	8	RESEARCH	1
0115	HR, BP response in patients	II	3	2	RESEARCH	2
0117	Achievement of Set HR in male volunteers	I	8	8	RESEARCH	3
0120	High and low slope increase in HR in patients with CAD	II	70	69	RESEARCH	4
0126	Functionality of Clinical Device system in volunteers	I	20	20	CLINICAL	4
0122	Efficacy and safety versus exercise with ECG diagnosis in patients with CAD	III	244	228	CLINICAL	4
0123	Efficacy and safety with echocardiography in patients with CAD	III	175	164	CLINICAL	4
0127	Efficacy and safety with radionuclide imaging in patients with CAD	III	151	148	CLINICAL	4
0128	Diagnostic specificity in patients with low risk of CAD	III	63	61	CLINICAL	4
0129	Safety and efficacy of "HOLD HR" feature in patients with CAD	III	64	61	CLINICAL	4
0130	Acute haemodynamic study	II	11	11	CLINICAL	4
0132	Safety and Efficacy in patients with CAD	IIIB	54	52	CLINICAL	4
0135	Describe effect of ESA and exercise stress on selected hormones and substrates, oxygen uptake and ventilatory parameters	IIIB	10	10	CLINICAL	4
0136	Performance with ECG, Echocardiography and sestamibi to diagnose CAD	IIIB	40	38	CLINICAL	4
0137	Evaluate ESA use with two different lead configurations	I/IIIB	101 (38 Vol) (63 pts)	96	CLINICAL	4
0138	Describe device performance (i.e. Target, slope, HOLD HR) and clinical utility of alerts/alarms	IIIB	99	92	MARKET	5
0139	Safety and performance in producing diagnostic signs of ischemia	IIIB	49	40	MARKET	5
0140	Effect of arbutamine and dobutamine stress on myocardial lactate extraction	II	10	9	MARKET	5
0141	System safety, and Investigator assessment of clinical utility for conducting stress test	IIIB	1070	867	MARKET	5
0142	Efficacy and Safety when used with echocardiography to identify viable myocardium in patients following acute MI	II	25	21	MARKET	5

- the ability of the ESA System to adequately control HR Slope (rate of rise of HR) and up to but not exceeding the HR Target according to the CLA objectives;
- the clinical utility of the ESA System alerts and alarms;
- the character and frequency of device malfunctions and errors of operation.
- the ability of the HOLD HR feature of the ESA System to maintain HR during stress testing for a maximum of 5 minutes.

The latest version of the CLA, which is also the version incorporated into the final GenESA®, is Revision 5 (Rev. 5). The clinical evaluation of the market prototype GenESA® Device incorporating CLA Revision 5 in a large population is study 0141 which involves 1070 patients. The performance of the CLA was evaluated by three variables: HR target, HR slope, and hold HR function.

HR Target Reached

HR Target is the maximum value that the heart rate should reach. In study 0141, 263 tests resulted in HR Target reached. Of the 263 tests, 216 were considered evaluable for HR Target reached. The mean (± SD) difference from HR Target was 0.5 ± 3.3 bpm with a range of -7 to 23 bpm. None of the patient with the HR Target reached experienced any adverse events associated with the GenESA® System test.

Control of HR Slope

The HR Slope was selected for each test by the investigator as either low (4-6 bpm/min), medium (7-9 bpm/min) or high (10-12 bpm/min). If the HR Slope was changed during the test, the primary HR Slope during drug delivery was chosen for analysis. For study 0141, 677 tests were considered evaluable for HR Slope. The results were the following:

Table 5
HR Slope results from clinical study 0141

slope (bpm/min)	Low (4-6)	Medium (7-9)	High (10-12)
N	163	351	163
Mean achieved HR slope	4.9 ± 2.6	6.8 ± 3.0	7.2 ± 2.8

Hold HR

The performance of the hold feature will largely depend on the dynamic response of each patient to the drug and the momentum present in the patient just before the HOLD was requested. The results from study 0141 are the following:

Evaluable periods (N)	141
Mean deviation from hold HR target (bpm)	-0.1 ± 5.0,
range (bpm)	-12 to 14
Mean maximum deviation from hold HR Target	4.9 ± 6.9,
range (bpm)	-9 to 24

In study 0141, all blood pressure and HR alerts (788) and alarms (431) activated at the appropriate conditions.

The results of the clinical studies to investigate the effectiveness of the GenESA® System (as a combination product) are presented in the GenESA® NDA 20-420. For estimates of sensitivity, specificity and predictive values, please refer to the "Clinical Trials" of the GenESA® (Arbutamine) Package Insert.

XII. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General Hospital and Personal Use Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISIONS

CDRH has determined that, based on the data submitted in the PMA and the NDA, there is reasonable assurance that the GenESA® device is safe and effective for its intended use. CDRH issued an approval order on SEP 12 1997.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling

Warnings, Hazards to Health from Use of the Device: See Warnings and Precautions in the GenESA® System Direction for use and the GenESA® (Arbutamine) Package Insert

Postapproval Requirements and Restrictions: See approval order

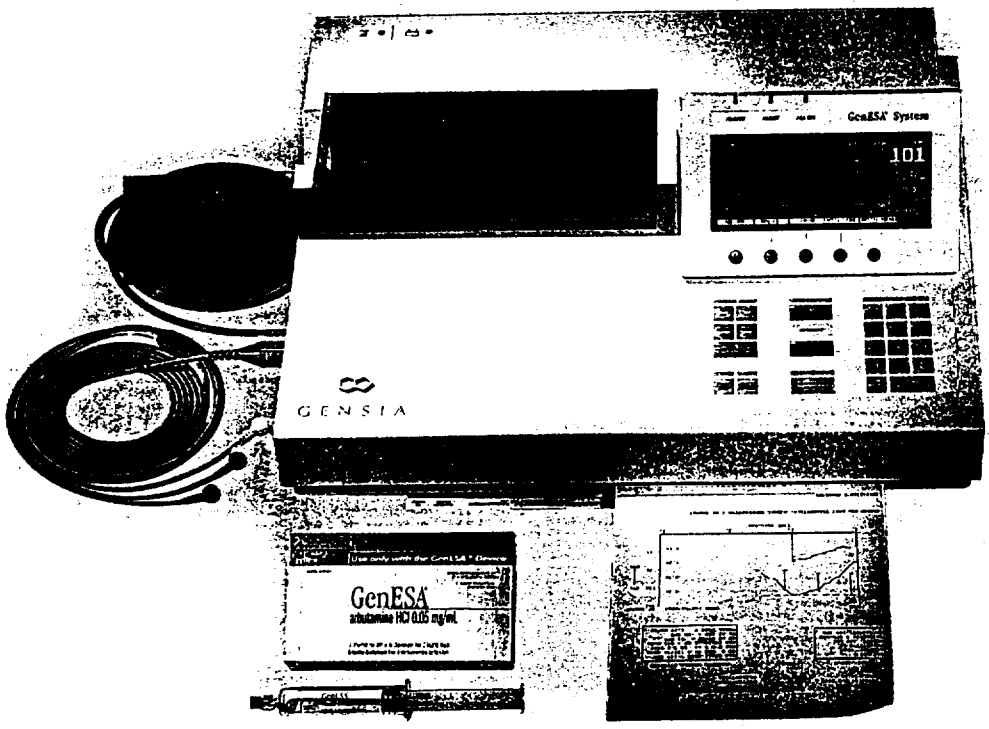
21

GENSIA
AUTOMEDICS™

For use with GenESA® (Arbutamine HCl Injection) 0.05 mg/mL

The GenESA® System

Directions For Use



Gensia Automedics, Inc.
Professional Services Dept.
9360 Towne Centre Drive
San Diego, CA 92121
1-800-788-7999

Caution: Federal law restricts this device to sale by or on the order of a physician.

Guide to Using this Manual

SECTION 1

Introduction to the GenESA System and Test

SECTION 2

How to Run a GenESA Test

SECTION 3

How the GenESA Device Works

APPENDIX A

Alerts/Alarms

APPENDIX B

Quick Reference Guide

APPENDIX C

Servicing

APPENDIX D

Guide to Using this Manual

Organization and Content:
This Directions for Use manual is composed of 3 sections and 4 appendices. The section names and a brief description of their content follow.

Section 1 – Introduction to the GenESA System and Test
This section provides an overview of the GenESA System and describes the indications and usage, contraindications, warnings and cautions. Its use as a pharmacological stress test and aspects of safety are reviewed. Personnel training requirements are briefly explained.

Section 2 – How to Run a GenESA Test
This section guides you through the GenESA Test, step by step. A detailed, push-this-button-next procedure is provided for the clinician who is unfamiliar with the GenESA Device. The steps start with system set-up, pre-drug delivery and patient preparation, then continue through entering patient data and starting the GenESA Test. These instructions provide information on how to monitor and change screen displays and GenESA Test parameters as well as explaining how to end the GenESA Test and print out the results. Following this detailed tutorial, five examples of typical test situations are presented.

Section 3 – How the GenESA Device Works
This is a reference section that provides information on device set-up requirements and describes in detail the operation of each light, keypad key, menu and softkey on the GenESA Device. This section identifies the location of user controls and device connectors. Drawings are also used to show the result of each key press in the menu-driven softkey system. An overview of the Alert/Alarm system is also provided. The Table of Contents should be used in order to find the appropriate page reference.

Appendix A – Alerts/Alarms Table
This section provides a table of information on Alerts/Alarms including: 1) the actual Alert/Alarm message, 2) the probable cause of the Alert/Alarm message, and 3) the appropriate corrective action to take in response to the Alert/Alarm.

Appendix B – Quick Reference Guide
This section includes a copy of the Quick Reference pull-out cards located on the GenESA Device. These cards provide information on: Basic Operating Instructions, Patient Connections, Alert/Alarm Reference, Gensia Automedics Assistance/Printer Care, and User Controls.

Appendix C – Servicing
This section contains information on the care and maintenance of the GenESA Device including detailed instructions for reloading paper, replacing the ribbon, and clearing paper jams from the printer. Use of the SERVICE submenu for calibration and verification of device operation is described. There is a list showing whom to contact to obtain service for the GenESA Device or to obtain technical/clinical support information.

Appendix D – GenESA Device Accessories and Reorder Information
This section lists the supplies and accessories used with the GenESA Device. Description of the items and reorder information is provided.

Use of Notes, Cautions and Warnings

Throughout this manual, special paragraphs will alert you to NOTES, CAUTIONS and WARNINGS.

NOTE

NOTES emphasize certain information to ensure clarity. For example, these Directions For Use show device functions, softkey labels, hardkey labels, and alert/alarm messages in capital letters for clarity (Start, Stop, Main Menu, etc.).

CAUTION

CAUTION statements identify conditions or practices that could result in damage to the equipment or other property.

WARNING

WARNING statements identify conditions or practices that could result in personal injury to the patient or the operator.

Abbreviations

The following abbreviations are used throughout this manual.

AC	Alternating Current
BP	Blood Pressure
BPM	Beats Per Minute
BPM/MIN	Beats Per Minute per Minute (Heart Rate Slope)
CAD	Coronary Artery Disease
DC	Direct Current
ECG	Electrocardiogram
HR	Heart Rate
Hz	Hertz (cycles per second)
IV	Intravenous
LED	Light Emitting Diode (Light)
µg	Micrograms
mL	Milliliters
mmHg	Millimeters of Mercury
mm/sec	Millimeters per Second
mV/cm	Millivolts per Centimeter
NIBP	Non-Invasive Blood Pressure
PC	Personal Computer
PSI	Pounds per Square Inch of Pressure
PxR or PRP	Systolic Blood Pressure X Heart Rate (Pressure Rate Product)
µg/kg/min	Micrograms per kilogram per minute

SECTION 1

Introduction to the GenESA System and Test

GENSIA AUTOMEDICS HAS DEVELOPED THE GenESA SYSTEM FOR USE IN THE EVALUATION OF PATIENTS WITH SUSPECTED CORONARY ARTERY DISEASE. THIS SECTION PROVIDES A DESCRIPTION OF THE GenESA SYSTEM COMPONENTS AND GIVES AN OVERVIEW OF THE GenESA TEST.

Overview of the GenESA System

The GenESA® System comprises the cardiac stress agent GenESA® (arbutamine) and its dedicated drug delivery device, the GenESA® Device. Arbutamine is a catecholamine with potent chronotropic and inotropic properties. Arbutamine is intended for direct intravenous infusion ONLY with the GenESA Device. The GenESA Device is a closed-loop delivery system which automatically adjusts the infusion rate using heart rate (HR) as the feedback parameter to increase HR towards a maximum HR limit (HR Target) at the rate of rise (HR Slope) set by the physician. The GenESA Device also includes the user interface, monitoring, and safety alarm systems.

This section provides an overview of GenESA (arbutamine), its infusion device, and the GenESA Test.

Indications and Usage

The GenESA System delivers arbutamine, a catecholamine, through a closed-loop, computer-controlled drug-delivery system to elicit acute cardiovascular responses similar to those produced by exercise. In patients with suspected coronary artery disease (CAD) who cannot exercise adequately, stress induction with the GenESA System is indicated as an aid in diagnosing the presence or absence of CAD.

The effectiveness of the GenESA System has been demonstrated in clinical studies using radionuclide myocardial perfusion imaging to predict the results of coronary angiography. These studies were in patients with high and lower risks of CAD and utilized blinded, central reading of images. Estimates of sensitivity, specificity and predictive values are presented in the "Clinical Trials" section of the arbutamine Package Insert.

Although the effectiveness of the GenESA System was also assessed in similar clinical studies utilizing echocardiography to predict the results of coronary angiography, the blinded, central reading of the images from the lower-risk echocardiography study was technically inadequate. Estimates of sensitivity, specificity, and predictive values, based on the non-blinded readings of echocardiograms at the local study sites, are presented for the lower-risk patients (see Clinical Trials). For the study of high-risk patients, the estimates are based on valid, blinded, central reading of images.

Like exercise testing, cardiac stress testing with the GenESA System must always be performed under the direct supervision of a physician, and cardiac emergency equipment and supplies (defibrillator, intravenous β-blocker, etc.) must always be available. Arbutamine must not be administered without use of the GenESA Device.

The GenESA System is not intended for use as a therapeutic product. The GenESA Device is not intended for administration of any drug other than arbutamine.

Contraindications

Arbutamine is contraindicated in patients with idiopathic hypertrophic subaortic stenosis, in patients with a history of recurrent sustained ventricular tachycardia, in patients with congestive heart failure (NYHA Class III or IV), and in patients who have shown previous manifestations of hypersensitivity to arbutamine. The GenESA System must not be used in the presence of an implanted cardiac pacemeaker or automated cardioverter/defibrillator.

Warnings and Cautions

The following is a complete list of warnings and cautions that appear in this manual and should be understood by the operater. Also, the package insert included with each prefilled syringe should be referred to for a complete listing of drug related safety issues.

WARNINGS

- ***A "HR Saturation" alarm indicates that the maximum achievable HR response has been reached. The infusion CANNOT be restarted after this alarm since no further increase in HR is expected and the likelihood of clinically significant arrhythmias may be increased.***

- ***The user should be familiar with and refer to the GenESA® System Directions for Use manual for complete operating instructions.***

- ***The ECG waveform provided by the GenESA® Device is not of diagnostic quality. It is intended to monitor heart rate response only. A separate diagnostic-quality ECG system (conforming with AAMI EC-11 Standard for Diagnostic Electrocardiographs) must be used by the physician at all times to verify heart rate, monitor for arrhythmias, and evaluate signs of myocardial ischemia.***

- ***Do not use the GenESA Device with any drug other than arbutamine. Operation of the device or effect of other drugs have not been investigated.***

- ***This device is to be used only by physicians and medical personnel, under the direct supervision of a physician, who are trained in its use.***

- ***At all times, clinical judgment must be used to determine the appropriateness of continuing the GenESA Test. The ultimate responsibility for the safe use of this test lies with the clinician.***

- ***The GenESA Device is NOT designed to detect arrhythmias. When arrhythmias occur, observe the QRS marker on the display to verify proper QRS detection (a dashed marker indicates counted QRS complexes). If QRS complexes are not detected (R-wave has no dashed marker), heart rate will be undercounted. If heart rate is undercounted, drug delivery may increase inappropriately. Discontinue drug delivery during any arrhythmia where heart rate is undercounted.***

- ***The GenESA Device is not designed to detect arrhythmias. Therefore, the patient should be monitored by diagnostic-quality ECG systems at all times. The SUDDEN CHANGE IN HEART RATE alarm may activate for some tachyarrhythmias or bradycardia, but not for all of them.***

- *The GenESA Device does not stop drug delivery in the case of high systolic blood pressure. Clinical judgement must determine whether to continue the GenESA Test during a high systolic blood pressure alert.*

- *When activating the HOLD HEART RATE function, the patient's actual heart rate may continue to rise for a short time above the HOLD level, due to the presence of arbutamine already infused. Heart rate will return to the HOLD level and remain controlled there for the duration of the HOLD period. If HOLD functionality is anticipated, the HIGH HR SLOPE Selection (12 BPM/MIN) should be avoided in order to minimize the amount of HR rise following HOLD activation.*

- *Use only the pre-filled 20 mL syringe supplied by Gensia Automedics to administer arbutamine. Discard syringe after use.*

- *Use a dedicated IV line connected directly to the hub of a minimal dead space IV catheter (do not use "butterfly" catheters) to infuse arbutamine. Do not use stopcocks, or Y connections or connect any other infusion line to the arbutamine line, since unintended bolus delivery of arbutamine could result. If a second infusion line is needed (e.g., for injection of imaging agents), a dual lumen catheter with separate infusion and exit ports may be used.*

- *Use of the same arm for BP measurements and drug delivery will result in irregular drug delivery and may lead to unpredictable heart rate changes.*

- *Use only small dead space IV catheters (less than 0.25 mL). Larger volumes may create an excessive time delay between drug administration and physiologic response. As a result, poor heart rate control or drug overdose may occur.*

- *Use only the IV administration set specified or supplied by Gensia Automedics for use with the GenESA Device. Refer to the packaging instructions for proper setup.*

- *Do not PURGE IV SET when attached to patient. Air embolus or bolus drug delivery may result.*

- *Do not use the IV TEST when the IV Set is attached to the patient. Air embolus or bolus drug delivery may result.*

- *Position the GenESA Device level with or below the patient's IV site to prevent risk of siphoning arbutamine.*

- ***The device is not designed or intended to detect infiltrations and will not alarm in most infiltration conditions.***

- ***Disconnect the IV line when resolving an IV occlusion alarm. Failure to do so could result in an inappropriate bolus being administered to the patient.***

- ***Do not exert any force greater than 4 pounds by pulling or stretching on the IV administration set. Inappropriate force may cause disconnection of the IV tubing from the luer adapter or may cause an IV LINE OCCLUDED alarm (due to the force on the IV set being transmitted to the syringe and the syringe exerting pressure on the sensor in the syringe holder). Always ensure that the GenESA Device is close enough to the patient to avoid any undue tension in the IV administration set.***

- ***ECG electrode sites must be prepared well to result in an adequate R-wave with minimal electrical interference. Heart rate overcounting or undercounting may occur with poor site preparation and result in arbutamine infusion that is either over or under the appropriate dose rate. Select the lead (I, II, III) with the highest amplitude R-wave (minimum of 0.33 mV) and the least amount of noise.***

- ***Conductive parts of ECG cables or ECG electrodes may not touch other conductive or grounded parts.***

- ***Line isolation monitor transients may resemble actual cardiac waveforms and thus inhibit heart rate alarms. Keep ECG cable and leads away from line isolation monitors.***

- ***It is important to firmly seat both the flange of the IV syringe barrel and the thumb-press disc on the syringe plunger into the slots provided in the syringe holder and the pusher block. This prevents uncontrolled delivery of arbutamine due to siphoning.***

- ***If arbutamine is NOT being infused into the patient correctly (e.g., the IV line is not connected properly) care must be taken to resolve the problem, or a high heart rate event can occur due to incorrect infusion rates. To avoid incorrect infusion rates that could result in sudden heart rate changes, the following steps should be taken:***
  1. INTERRUPT the drug delivery.
  2. Reconnect the IV line properly.
  3. Wait one minute before restarting.
  4. ReSTART the drug delivery.

- *If an undetected equipment fault occurs (single fault condition), the maximum amount of drug delivered to the patient is 0.5 mL (25 µg).*

- *The BP cuff is not recommended for use on patients with less than 18 cm limb circumference.*

- *If any BP measurement is suspect while using the GenESA Device, another method of blood pressure measurement should be used to verify the reading. When auscultating to verify diastolic blood pressure, use the fifth phase of the Korotkoff sounds.*

- *When monitoring blood pressure at frequent intervals, observe the patient's limb distal to the cuff for signs of impeded blood flow.*

- *Maximum BP cuff inflation time is 2 minutes. Long cuff inflations may restrict blood flow to the arm or impede venous return.*

- *The GenESA Device must not be used for patient monitoring or IV drug delivery while in the Service mode.*

- *DANGER: Explosion risk if used with flammable anesthetics.*

- *Do NOT use the GenESA Device during electrosurgical procedures. High-intensity radio frequency energy can induce heat into electrodes and cables, causing burns. Heart rate and/or blood pressure measurement errors and damage to the equipment may also result.*

- *This device may interfere with ECG equipment. Monitor ECG equipment carefully when using this unit. Refer to page C.17 of this operator's manual for further information.*

- *To assure operator safety during defibrillation, keep the discharge paddles away from ECG and other electrodes, as well as other conductive parts in contact with the patient. For additional safety precautions on the use of the defibrillator, refer to the defibrillator operator's manual.*

- *Disconnect the GenESA Device from the AC power source before cleaning to avoid possible shock hazard or equipment damage.*

- *Use only "Hospital Grade" AC power receptacles. The GenESA Device's leakage current may not be within specification when using an improperly grounded power source.*

- *If a computer is connected to the GenESA Device, it must be located outside the "patient environment" a minimum of 1.5 meters, since the computer is not an approved medical device.*

- *The GenESA Device may not meet its performance specifications if stored or used outside the specified temperature and humidity ranges listed in the Appendix.*

- *Use care when replacing ribbon. The print head (located directly inside the printer cover) will be hot immediately after printing.*

- *DO NOT USE THE GenESA DEVICE following a reoccuring equipment malfunction as device performance may be compromised.*

CAUTIONS

- *For accurate ECG input and protection against noise and other interference, use only ECG electrodes and cables recommended or supplied by Gensia Automedics, and follow recommended application procedures. The GenESA System's ECG electrodes must be of similar metal to prevent excessive polarization. Electrode sites must be well prepared to ensure good R-wave detection. ECG trace recovery time after application of defibrillator pulses may be especially compromised.*

- *A minimum R-wave amplitude of 0.33 mV is recommended. If the R-wave signal amplitude is less than 0.33 mV an alert will activate indicating Low Amplitude ECG. This alert will prevent the start of the GenESA Test.*

- *After a defibrillator discharge, the ECG trace and heart rate display takes approximately 6 seconds to recover, before monitoring will resume.*

- *Battery power allows only 30 minutes of operation. While operating on battery power, the GenESA Device will alarm below 11.8 volts and will turn itself off when battery charge drops to 11.4 volts. To avoid serious damage to the battery, plug in the AC power cord to a live connection even when the GenESA Device is not in use.*

- *When AC power is lost, do not continue the GenESA Test without an active diagnostic ECG instrument connected to the patient. The GenESA Device only monitors HR and BP, but does not identify arrhythmias or indications of ischemia.*

- *Leaving the GenESA Device's lead-acid battery in a completely discharged state may result in permanent battery damage. The battery*

should be kept fully charged. To maintain battery charge, keep the GenESA Device plugged into AC power even when not in use. Note that the shelf life of a charged battery is 12 to 18 months.

- ***Do not use "KODAN TINKTUR FORTE" cleaning solution on the keypad. Stress cracks may result and keypad failure could occur.***
- ***Check that power is off before replacing ribbon. If the printer cover is removed with power still on, damage to the print head or platen may result. Carefully slide printer into device chassis to avoid damage to printer cables.***
- ***Do not use a damaged device or accessory.***
- ***Damage to the GenESA Device can result from applying voltages to the analog output cable wire.***

GenESA (Arbutamine)

This subsection briefly describes important features of the drug arbutamine. Full details including contraindications, warnings, adverse events and other drug related information are provided in the current Package Insert enclosed with each prefilled syringe and in the example insert included at the end of this manual.

Arbutamine is a potent beta adrenergic agonist producing both positive chronotropic (increase in HR) and inotropic (increase in contractility) responses. It is a weak alpha adrenergic agonist. Arbutamine is used as a cardiac stress agent to provoke myocardial ischemia secondary to its cardiac effects. Arbutamine increases cardiac work through its positive chronotropic and inotropic actions, while also probably limiting regional subendocardial perfusion and hence tissue oxygenation.

Mechanism of Action

By increasing chronotropic and inotropic actions, arbutamine acts as a cardiac stress agent to mimic exercise and provoke myocardial ischemia in patients with compromised coronary arteries. It also probably limits regional subendocardial perfusion, and hence tissue oxygenation, by its increase in heart rate (HR). The delivery system adjusts the rate of arbutamine delivery to achieve a selected increase in heart rate.

Arbutamine is a sympathomimetic that exhibits increased selectivity for β-adrenoceptors over α-adrenoceptors in functional assays. The β-agonist activity of arbutamine provides cardiac stress by increasing HR, cardiac contractility and systolic blood pressure.

Some α-receptor activity is retained in vivo, such that the degree of hypotension observed for given chronotropic activity is less with arbutamine than with isoproterenol, a specific β-agonist.

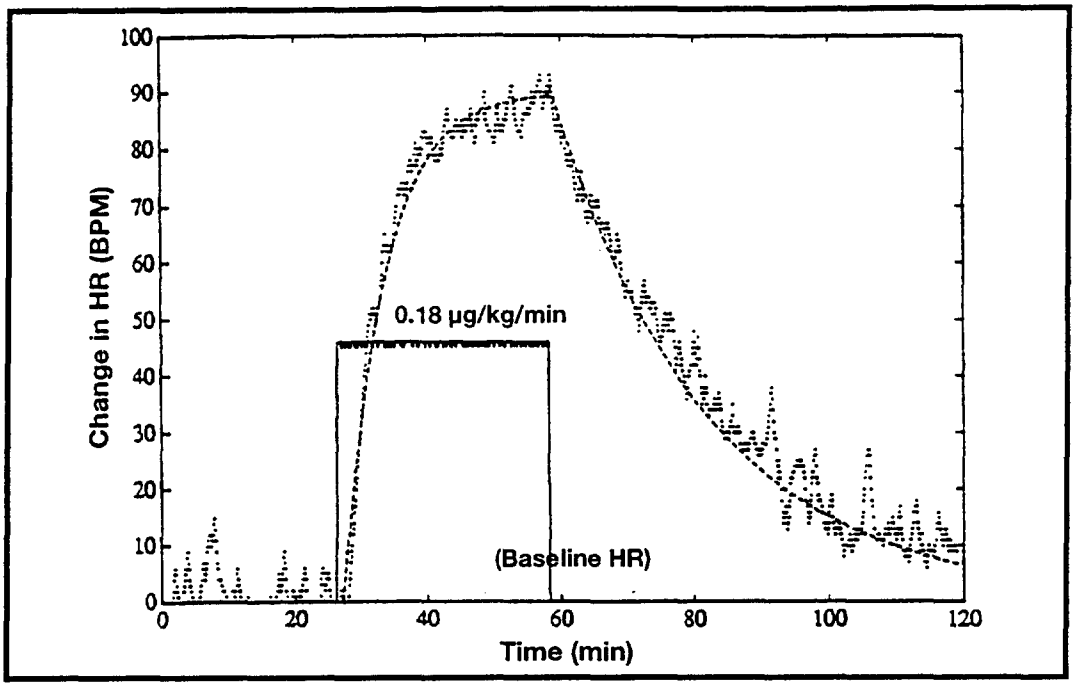


Fig. 1-1. Steady-State Infusion of Arbutamine.
Rate: 0.18 µg/kg/min Duration: 30 minutes.

Fig. 1-1 shows the typical HR response (in a normal volunteer) to a constant infusion of arbutamine. The time for a 50% decrease in HR, following termination of arbutamine infusion, is approximately 15 minutes. However, not all patients respond in the same way to arbutamine and there can be patient-to-patient variability in the amount of change and speed of change in HR. The GenESA Device is designed to automatically adjust the infusion rate of arbutamine to compensate for these variations.

A dose response curve for arbutamine is derived from clinical trial data where normal subjects received constant infusion rates. The steady-state HR response data at different rates determines the dose-response curve as shown in Fig. 1-2.

As expected, higher infusion rates result in increased HR response. It is noteworthy that the dose-response curve levels off at higher HR responses. This phenomenon has been termed "HR SATURATION." During a GenESA Test, it is possible that with increasing infusion rates, the HR will reach a maximum level. The GenESA Device will detect this event and trigger an alert. If the HR saturation continues, drug delivery will be interrupted by a "HR SATURATION" alarm (see Appendix A, page A.14 for details on time intervals). Infusion cannot be restarted after this alarm when the HR is greater than 40 BPM above baseline since no further increase in HR is expected and the likelihood of clinically significant arrhythmias may be increased. The HR range where the saturation occurs is dependent on the individual patient HR response and will only become evident during the test.

Dosage and Administration

Arbutamine must be administered from the prefilled syringe and must not be diluted or transferred to another syringe. Arbutamine is intended for direct intravenous infusion ONLY with the GenESA Device.

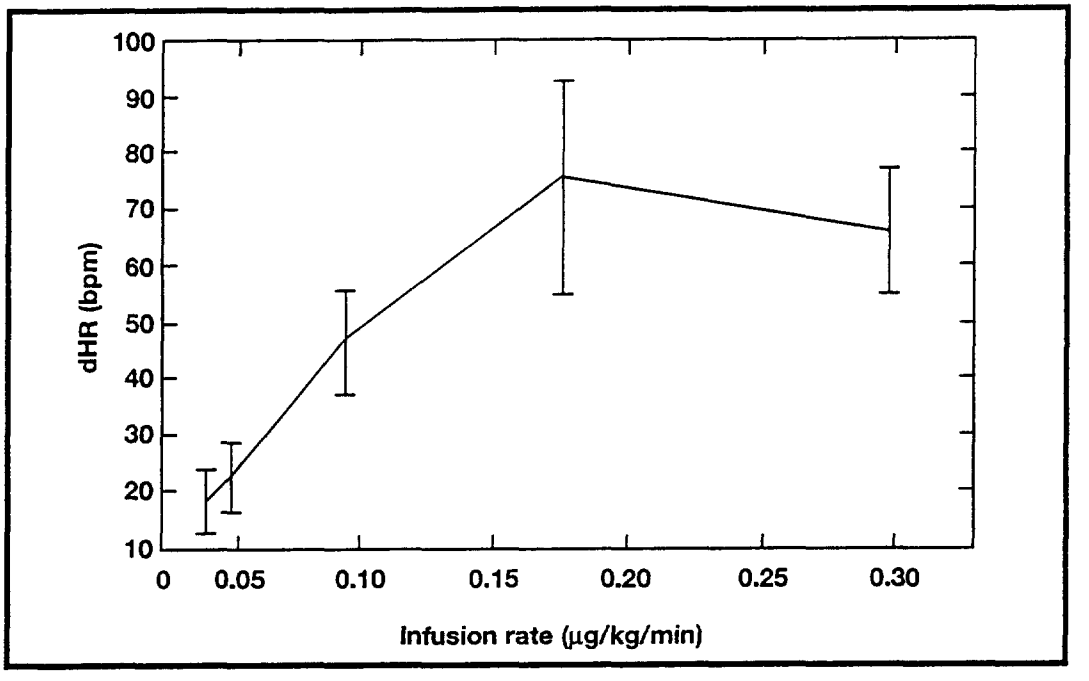


Fig. 1-2. Dose Response Curve for Arbutamine.

Arbutamine is supplied as a clear and colorless sterile solution for infusion in a 20 mL prefilled syringe containing 0.05 mg/mL of arbutamine. Arbutamine syringes should be stored refrigerated at temperatures between +2°C and +8°C.

NOTE

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

The GenESA Device individualizes the dosing of arbutamine based on the pharmacological response of each patient. The maximum infusion rate delivered by the GenESA Device is 0.8 µg/kg/min and the maximum total dose is 10 µg/kg.

The physician selects the maximum heart rate limit (HR TARGET) and rate of rise of heart rate (HR SLOPE). The choice of HR SLOPE should be based upon the desired duration of the test and the rate of HR rise, judged by the physician, to be most appropriate. Once started, the GenESA Device automatically controls drug administration. It monitors HR and blood pressure response, provides safety alerts and alarms for undesirable events, and stops the infusion when a potential safety hazard or HR saturation (a plateau in the HR response) occur, or when the HR TARGET is achieved.

The GenESA Device

The GenESA Device consists of two major components described below and illustrated in Figure 1-3. Device accessories included are 3 NIBP cuffs (small, standard, and large adult), BP tubing and ECG cable.

1. The **Monitoring System** provides controls for patient heart rate and blood pressure monitoring, a set of alerts and alarms to warn of potential problems, and a visual display to

indicate the patient's vital signs and trended test data. The user interface is menu driven using a set of five softkeys located on the display housing. The monitoring system communicates to a printer for documenting test results.

2. The **Drug Delivery System** consists of an IV syringe pump to infuse arbutamine at a rate determined by a sophisticated closed-loop feedback computer. This computer constantly receives patient heart-rate information and automatically adjusts the infusion rate to achieve the desired heart-rate response. Controls for the Drug Delivery System are located on the device keypad.

For additional information on the use of the GenESA Device please refer to Section 2 which describes "How to Run a GenESA Test" and Section 3 for a detailed description of "How the GenESA Device Works."

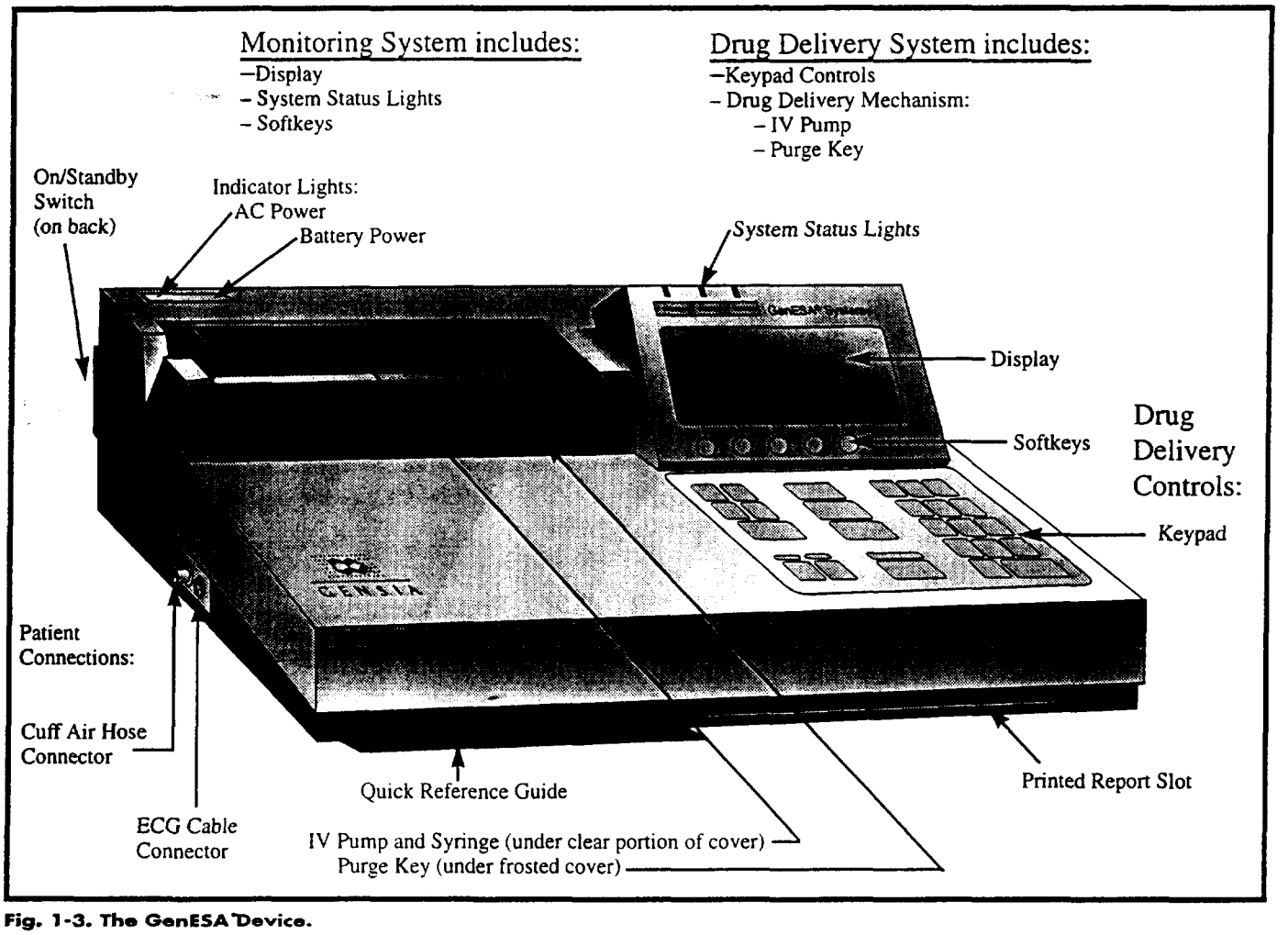


Fig. 1-3. The GenESA Device.

Patient Safety Issues

Alerts and Alarms

The GenESA Device does not make clinical decisions regarding patient safety. However, the GenESA Device does provide alerts and alarms for heart rate and blood pressure changes and other clinical situations. The alerts and alarms warn of a potentially hazardous condition, and, if appropriate, the System stops drug delivery.

Alerts are audible and visual messages to warn of conditions that should be corrected within a short time. Alerts do NOT stop drug delivery, although some alerts progress into alarms when the condition is not corrected in time. Alarms are audible and visual messages to warn of conditions that present possible hazards to patient or equipment. Alarms immediately stop drug delivery and provide messages that explain why. The event that triggers an alarm must be corrected before you can restart the GenESA Test.

The following patient hazard conditions will trigger an alert or alarm. Please refer to Appendix A for a detailed listing of all alert and alarm conditions.

Sudden Changes in Heart Rate

If the HR increases or decreases by 20 BPM or more in a 10-second period, an alert indicates SUDDEN CHANGE IN HEART RATE. You can silence the alert tone and continue the test. However, if the condition persists for an additional 30 seconds, an alarm with the same message is activated and drug delivery is stopped.

WARNING

The GenESA Device is NOT designed to detect arrhythmias. Therefore the patient should be monitored by diagnostic-quality ECG systems at all times. The SUDDEN CHANGE IN HEART rate alarm may activate for some tachyarrhythmias or bradycardia, but not for all of them.

Rapid Heart Rate Response

Some patients may respond to arbutamine with a heart rate increase that is greater than selected. If this occurs, the control algorithm automatically reduces the infusion rate.

If the average heart rate is greater than 10 BPM above the expected value, based upon the selected HR SLOPE, an alert is activated: RAPID INCREASE IN HEART RATE.

If the patient's heart rate persists at that high level for one and one half minutes (or if at any time the average heart rate is greater than 20BPM above the expected value), an alarm is activated: HEART RATE RISE TOO FAST and drug delivery is stopped automatically. The alert and alarm for rapid increase in HR response are not active during operation of the HOLD HEART RATE feature.

Heart Rate Saturation and Declining Heart Rate

Prior to reaching the maximal HR limit (HR Target) or other test endpoint, some patients may reach a maximum HR response to arbutamine (see dose-response curve on page 1.4). When the device detects that there is no continued increase in HR (despite increasing infusion rates), a POSSIBLE HR SATURATION, NO INCREASE IN HEART RATE, INCREASING IV DOSE alert will be triggered. If this condition persists, the alert will transition into an alarm and drug delivery will be interrupted. An alarm will also be activated if the average HR

decreases by 10 BPM or more (15 BPM in the HOLD HEART RATE mode), or if both the declining HR alert and the falling systolic blood pressure alert are active at the same time.

The alarm displayed depends upon the level of HR increase achieved. If the HR is 40 BPM or less above baseline then the message line will indicate NO INCREASE IN HEART RATE, INCREASING IV DOSE, RESTART IF CLINICALLY APPROPRIATE and restart is allowed. If the patient's HR is greater than 40 BPM over baseline, then the HR saturation alarm message will indicate HEART RATE SATURATION, DO NOT RESTART, HR INCREASE GREATER THAN 40 BPM and restart is prevented. In this case, the patient has reached a point on the dose-response curve where continued dosing with arbutamine is unlikely to elicit further increase in HR. Achieving HR saturation is a diagnostic endpoint of the GenESA Test. For further information regarding the function of these alerts and alarms see page A.14.

Hypotension

If systolic blood pressure falls significantly between two consecutive measurements, an alert is activated: FALLING SYSTOLIC BLOOD PRESSURE. At this point, if clinically appropriate, you may manually STOP drug delivery. If the next blood pressure measurement after the alert still indicates falling systolic blood pressure, an alarm is issued with the same message, and the GenESA Device stops drug delivery. If any single measurement of systolic blood pressure is 25% lower than the last measured value (or if systolic blood pressure falls below 90 mmHg), the alarm is immediately activated and drug delivery is stopped.

Hypertension

Any test that increases cardiac function (by increasing heart rate, contractility or systolic blood pressure) may present a concern, particularly for patients with high blood pressure. For that reason, the GenESA Device allows you to set a high systolic blood pressure alert limit. If this high systolic value is exceeded, an alert indicates: HIGH SYSTOLIC PRESSURE LIMIT EXCEEDED.

As a further precaution, if there is a 35% increase in systolic blood pressure (for pressures above 130 mmHg) from one BP measurement to the next, the GenESA Device alerts: RISING SYSTOLIC BLOOD PRESSURE.

WARNINGS

- ***The GenESA Device does NOT stop drug delivery in the case of high systolic blood pressure. Clinical judgement must determine whether to continue the GenESA Test during a high systolic blood pressure alert.***

- ***If any BP measurement is suspect while using the GenESA Device, another method of pressure measurement should be used to verify the reading. When auscultating to verify diastolic pressures, use the fifth phase of the Korotkoff sounds.***

The GenESA Test

This subsection gives an overview of the three GenESA Test phases shown in Fig. 1-4. For precise operating instructions and examples, see Section 2, "How to Run a GenESA Test".

Pre-Drug Phase

The patient is provided with an explanation of what will happen during the GenESA Test. The Operator attaches the ECG leads and BP cuff to the patient. The prefilled drug syringe is placed into the IV pump and the IV line is prepared.

NOTE

The patient should be advised that, during the GenESA Test, he/she may become aware of their heart beating rapidly and forcefully. This is likely to be similar to the awareness of a rapid and forceful heartbeat during and immediately following exercise, but without the associated fatigue and increased respiration. This awareness is to be expected during a GenESA Test.

Baseline HR monitoring begins after ECG leads are attached and an ECG signal is detected. A manually initiated BP measurement must be taken. The operator enters patient information. Age and Weight are required while Gender, Height and Patient ID are optional. The operator then selects the heart rate slope (HR SLOPE) and the maximum heart rate limit (HR TARGET).

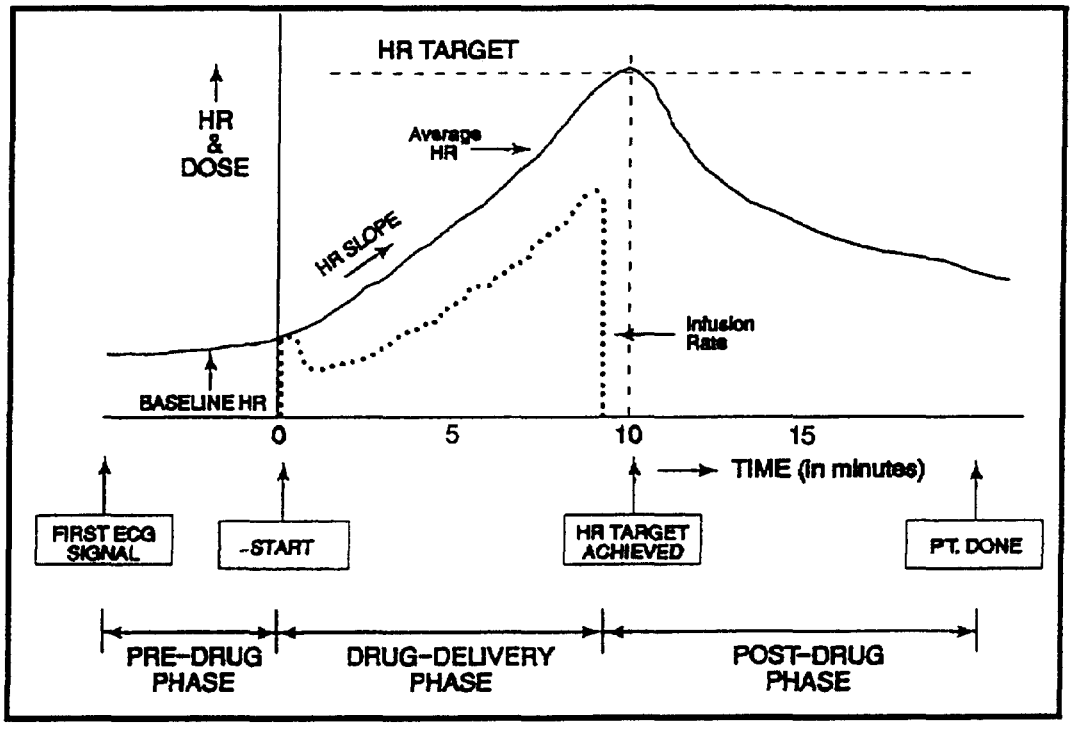


Fig. 1-4. Three Phases of a GenESA Test.

Drug Delivery Phase

This phase begins when the START key is pressed, and continues until STOP is pressed or the device interrupts the infusion. The GenESA Device automatically adjusts the infusion rate to achieve the selected heart rate response.

At the beginning of the GenESA Test the device administers a fixed dose of 0.1 ug/kg/minute for one minute. Following this is a 2-3 minute period of closed loop control initialization to begin the HR rise. Then, the HR Slope is controlled until the selected HR Target or other end-

point is achieved. During the infusion, the HOLD HEART RATE feature can be utilized in order to maintain the patient's HR close to its current level for up to five minutes.

Post-Drug Phase

Termination of drug delivery can occur automatically when the maximal HR limit (HR Target) is reached or due to an alarm (eg: HR saturation) or the manual use of the STOP key. Endpoints that define the completion of a GenESA Test and the beginning of the recovery (post-drug) phase are:

- Reaching the selected maximal HR limit (HR Target). It should be noted that the closed-loop algorithm controls the infusion of arbutamine to approach, but not to exceed, this maximal limit;

- Reaching the maximum HR response to arbutamine (HR saturation). This represents reaching the point on the dose-response curve where continued dosing with arbutamine fails to elicit any further increase in HR. The GenESA Device identifies this phenomenon and provides appropriate alerts and alarms to warn the physician. In the majority of patients, the occurrence of HR saturation represents the achievement of an adequate level of stress;

- Use of the STOP key because of the development of myocardial ischemia (e.g., ECG or echocardiographic evidence) or intolerable symptoms (e.g., angina).

Heart rate and blood pressure continue to be monitored during the post-drug phase, as they return toward the pre-drug values.

NOTE

The Post-Drug phase can begin, not only after achieving an appropriate test endpoint, but also at any time during drug delivery if the arbutamine infusion is interrupted or stopped for any reason. Activation of an alarm automatically puts the GenESA Test into the Post-Drug Phase until the alarm is resolved. If the alarm is resolved, and if clinically appropriate, the Drug Delivery Phase can be resumed by pressing the START key.

Operator Training Requirements

Gensia Automedics recommends that all operators undergo training in the use of the GenESA System prior to operation of the GenESA Device.

WARNING

This device is to be used only by physicians and medical personnel, under the direct supervision of a physician, who are trained in its use.

As a minimum, each operator should review and be thoroughly familiar with the following:

- This Directions for Use Manual.
- GenESA (arbutamine) Package Insert.
- Other GenESA System training materials.
- Set-up of the ECG electrodes.
- Preparation and set-up of the IV administration site.
- Use of the blood pressure and heart rate (R-wave) monitor.
- Operation of the keys that control drug delivery to the patient.

Additional training materials and assistance in the correct use of the GenESA System can be obtained from Gensia Automedics.

For More Information

For clinical information, device service information or to report a patient safety problem call 1-800-788-7999 between the hours of 6:00 a.m. to 5:00 p.m. Pacific time.

Mailing Address: Gensia Automedics, Inc.
Professional Services Dept.
9360 Towne Centre Drive
San Diego, CA 92121

Y36-105-G02

GenESA®

arbutamine HCl 0.05 mg/mL

Sterile Solution for Intravenous Infusion
with the GenESA® Device

DESCRIPTION

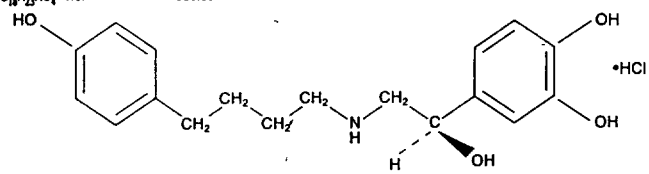
GenESA® (arbutamine hydrochloride, sterile solution for intravenous infusion, 0.05 mg/mL) is a synthetic catecholamine with chronotropic and inotropic properties. Chemically, arbutamine hydrochloride is (R)-4-[1-hydroxy-2-[[4-(4-hydroxyphenyl)-butyl]amino]ethyl]-1,2-benzenediol hydrochloride.

Arbutamine hydrochloride is an off-white amorphous solid, which is freely soluble in water and ethanol, but is practically insoluble in diethyl ether and hexane. It has the following structural formula:

CHEMICAL STRUCTURE

Molecular formula: $C_{18}H_{23}NO_4 \cdot HCl$

Molecular weight: 353.85



GenESA (arbutamine hydrochloride, sterile solution for intravenous infusion, 0.05 mg/mL) is formulated in an isotonic, buffered vehicle (pH 3.8) in a 20 mL prefilled syringe.

Active Ingredient: Arbutamine Hydrochloride 0.05 mg/mL.

Inactive Ingredients: Sodium Metabisulfite, NF 0.10 mg/mL, Citric Acid Monohydrate, USP 1.40 mg/mL, Trisodium Citrate Dihydrate, USP 0.88 mg/mL, Sodium Chloride, USP 8.50 mg/mL, Disodium Edetate, USP 0.10 mg/mL, and Water for Injection, USP q.s. ad 1.0 mL. The air in the prefilled syringe has been replaced by Nitrogen, NF.

The GenESA® System comprises the cardiac stress agent GenESA (arbutamine hydrochloride) and a drug delivery device, the GenESA® Device. GenESA is intended for direct intravenous infusion ONLY with the GenESA Device. The "GenESA System Directions for Use", a detailed instruction manual provided with each GenESA Device, provides an overview of the GenESA System, full details on how to conduct a pharmacological stress test using the GenESA System, and detailed information on the operation and function of the GenESA Device (see also **DOSAGE AND ADMINISTRATION**).

CLINICAL PHARMACOLOGY

Mechanism of Action

By increasing cardiac work through its positive chronotropic and inotropic actions, arbutamine acts as a cardiac stress agent to mimic exercise and provoke myocardial ischemia in patients with compromised coronary arteries. It also probably limits regional subendocardial perfusion, and hence tissue oxygenation, by its increase in heart rate (HR). The delivery system adjusts the rate of arbutamine delivery to achieve a selected increase in heart rate.

Arbutamine is a sympathomimetic that exhibits increased selectivity for β-adrenoceptors over α-adrenoceptors in functional assays. The β-agonist activity of arbutamine provides cardiac stress by increasing HR, cardiac contractility and systolic blood pressure.

Some α-receptor activity is retained in vivo, such that the degree of hypotension observed for given chronotropic activity is less with arbutamine than with isoproterenol, a specific β-agonist.

Effects on HR and Blood Pressure

In clinical studies of patients (N=494) with known or suspected coronary artery disease (CAD), GenESA was delivered using the GenESA Device to achieve an identified maximum HR unless an endpoint (pain, ECG changes) was attained sooner. Under these conditions the mean maximum increase in HR was 52 bpm and the mean maximum increase in systolic blood pressure was 36 mmHg.

After termination of arbutamine infusion, HR decreased, with 50% of the HR increase gone by 16 minutes (N=315).

The GenESA System can be programmed to give different rates of HR increase (HR Slope). The maximum increases in HR and systolic blood pressure were independent of the selected rate of HR increase. In patients who underwent a formal comparison of GenESA and exercise testing, effects on HR and BP were similar.

The effects of arbutamine on HR and systolic blood pressure are attenuated by concurrent administration of selective and non-selective β-blockers. Depending on the β-blocker, evidence of this attenuation is still present 23 hours after the last dose. In patients in whom β-blockers had been withdrawn for a minimum of 48 hours prior to receiving arbutamine, the HR and systolic blood pressure responses to arbutamine were similar to those seen in patients who had not received β-blockers for at least 2 weeks prior to arbutamine.

In 19 patients (12 with, and 7 without, a stenosis ≥ 50% in 1 or more major coronary arteries) the cardiac hemodynamic effects of arbutamine were assessed using invasive techniques. Cardiac contractility (left ventricular dP/dt), cardiac output (measured by thermodilution) and total systemic vascular resistance (SVR) were determined at low stress (a mean HR increase from baseline of 25 bpm) and at peak stress (a mean HR increase from baseline of 40 bpm). At low stress, cardiac contractility and output had increased by 66% and 45%, respectively, from baseline, and they rose to 80% and 63% above baseline at peak stress. Total SVR decreased from baseline by 41% at low stress and by 48% at peak stress.

By 15 minutes after the end of the infusion, cardiac contractility and SVR were within approximately 15% of baseline, and cardiac output was 29% above baseline.

Left ventricular ejection fraction (LVEF), assessed by echocardiography, was evaluated in a study of 156 patients with known or suspected CAD tested using arbutamine infusion and exercise. With an increase in HR from baseline of approximately 20 bpm, the relative increase in LVEF was 22%. At the end of the arbutamine infusion, when the mean increase in HR from baseline was 59 bpm, the relative increase in LVEF was 23%. By comparison, the relative increase in LVEF at the end of exercise was 14%.

Pharmacokinetics and Metabolism

Because of sensitivity limitations of the arbutamine assay, the pharmacokinetics of arbutamine in humans have been characterized only for the first 20-30 minutes after the termination of intravenous infusions up to 0.3 μg/kg/min. In a study in 12 healthy men, the half-life was about 8 minutes, plasma clearance about 4 L/hr/kg, and volume of distribution 0.74 L/kg. Plasma protein binding is approximately 58%. Arbutamine is mainly (>75%) eliminated by metabolism, principally to methoxyarbutamine, which is excreted in free or conjugated form in urine. Ketoarbutamine has been tentatively identified as another metabolite. Following intravenous infusion of 14C-arbutamine to healthy men, 84% of the total radioactivity was excreted in the urine within 48 hours, with 9% excreted in feces. Total radioactivity in plasma declined with a half-life of 1.8 hours, probably due to metabolites with longer half-lives than arbutamine. The rapid onset of effect on heart rate after start of arbutamine infusion (approximately 1 minute) and the rapid decline in heart rate following termination of infusion of arbutamine (time for a 50% decrease is 13-16 minutes) suggest that the pharmacological activity resides primarily with the parent compound and not with any of its more long-lived metabolites. Pharmacokinetics have not been characterized in women, the elderly, or different racial groups.

54

Clinical Trials

The usefulness of diagnostic tests can be defined in various ways. Measures of sensitivity (ability of test to identify diseased patients, in this case the rate of positive stress tests in patients with positive angiograms, or true positives divided by true positives plus false negatives) and specificity (ability of test to identify people without disease, in this case the rate of negative stress tests in patients with negative angiograms, or the true negatives divided by true negatives plus false positives) are frequently used. The problem is that the usefulness of a test can depend not only on sensitivity and specificity but on prevalence of the disease. Thus, for example, even a very sensitive test will be of minimal use in a population where almost all patients have the disease; for example, if 100% of patients have the disease, even 90% sensitivity will mean an "error rate" (declaring no disease when disease was present) in 10% of patients. In addition to sensitivity and specificity, therefore, tests are often described in terms of positive predictive fraction (the rate of correctness of a positive test) and negative predictive fraction (the rate of correctness of a negative test).

In clinical studies, patients underwent coronary angiography and GenESA System testing with radionuclide perfusion imaging (using thallium-201 or technetium-99m sestamibi) or with echocardiography. For purposes of these studies, an angiogram was considered positive if it demonstrated at least one ≥ 50% diameter stenosis of a major coronary artery; the GenESA System test was considered positive if perfusion defects were seen by radionuclide imaging or if wall motion abnormalities were noted on echocardiography, at baseline or during stress.

First for perfusion imaging and second for echocardiography, the following discussion gives both (1) a sensitivity/specificity/positive and negative predictive value analysis for two studies (one in patients with a high risk for CAD, one with a lower risk) and (2) an overall analysis that relates the information provided by the test relative to a prior estimate (based on a standard algorithm) of the likelihood of CAD being present.

1. Perfusion Imaging: Sensitivity/Specificity

The ability of radionuclide tests to predict the results of coronary angiography was assessed in 234 patients enrolled in two studies. In the high-risk study, patients were selected based on coronary angiographic evidence of CAD obtained within 12 weeks prior to the GenESA System test with thallium imaging. Patients were also included if coronary angiography was scheduled within 4 weeks following the GenESA System test. All studies were read without knowledge of other results. In the lower-risk study, patients were selected if coronary angiography had been performed within 12 weeks before or after the GenESA System test with thallium or sestamibi imaging, and results were re-read blindly after the study to give a similar assessment of the test. The results are shown in Table 1.

Table 1
Sensitivity, Specificity and Predictive Fractions for Radionuclide Imaging with the GenESA System

Study	Sensitivity	Specificity	Positive Predictive Fraction	Negative Predictive Fraction
High Risk	97/112 (87%)	2/8 (25%)	97/103 (94%)	2/17 (12%)
Lower Risk	51/81 (63%)	21/33 (64%)	51/63 (81%)	21/51 (41%)
Thallium	10/16 (63%)	7/12 (58%)	10/15 (67%)	7/13 (54%)
Sestamibi	41/65 (63%)	14/21 (67%)	41/48 (85%)	14/38 (37%)

Note that although sensitivity and specificity are in general independent of prevalence, it is possible that in this case prevalence (or, more likely, the presence of various factors related to CAD) does influence the test results, e.g., by giving more false positives in the high risk group (and thus lower specificity).

Note also that in a very high-risk group, use of the test may give less than satisfactory overall advice although (see next section) the ability to predict the results of angiography in any given patient may be improved. Thus, even with a high sensitivity of 87%, 15/112 patients with CAD were identified as not having it, and of 8 patients without CAD, 6 were identified as having it. The test is most helpful where the likelihood that the patient has arterial disease is neither very high nor very low.

2. Perfusion Imaging: Predictive Value of the GenESA System Test

Another approach to considering results of GenESA System testing is to describe the impact of the test result on the estimated likelihood of CAD based on the patients' defined risk, utilizing all available data about the patient. Using an algorithm developed by Pryor, DB, et al. (Am J Med 1983; 75:771-80), the 233 patients with demographic data available who underwent coronary angiography and GenESA System testing assessed with perfusion imaging were categorized as having a low (<20%), intermediate (20-80%) or high (>80%) likelihood of CAD. The characteristics of the three groups are summarized in Table 2 below.

Table 2
Characteristics of 233 Patients Who Each Underwent Coronary Angiography and had a GenESA System Test Assessed with Radionuclide Imaging

Pretest CAD likelihood Group called % (N) of Patients	<20% "Low" 4% (9)	20-80% "Intermediate" 21% (50)	>80% "High" 75% (174)
Age 65 years	11% (1)	18% (9)	36% (63)
Male	22% (2)	64% (32)	86% (150)
Typical Angina	0% (0)	14% (7)	74% (128)
Atypical Angina	11% (1)	25% (50)	20% (34)
Hyperlipidemia	33% (3)	54% (27)	59% (102)
Diabetes	33% (3)	16% (8)	29% (51)
Smoking	33% (3)	32% (16)	45% (78)
Prior MI	0% (0)	18% (9)	51% (88)
MI on ECG	0% (0)	0% (0)	20% (35)
ST-T Abnormality	22% (2)	16% (8)	30% (52)
# Patients with:			
1 Risk Factor	33% (3)	6% (3)	0% (0)
2 Risk Factors	67% (6)	28% (14)	6% (10)
3 Risk Factors	0% (0)	44% (22)	18% (32)
4 Risk Factors	0% (0)	22% (11)	29%(51)
≥5 Risk Factors	0% (0)	0% (0)	47% (81)
Mean (±SD) # Risk Factors/Patient	1.7±0.5	2.8±0.8	4.5±1.4
Angiography positive	33% (3)	56% (28)	78% (135)

As summarized in **Table 3** below (and as would be seen with any other less-than-perfect test), the performance of the GenESA System varied from one subgroup to another; it was most uniformly accurate in patients with an intermediate pre-test likelihood of disease.

Table 3
Predictive Value of GenESA System Testing when used with Radionuclide Imaging

Pretest probability of positive angiogram	N	Positive GenESA Test	Positive GenESA test was correct (angiogram positive)	Negative GenESA Test	Negative GenESA test was correct (angiogram negative)
Low	9	3 (33%)	0 (0%)	6 (67%)	6 (100%)
Intermediate	50	28 (56%)	22 (79%)	22 (44%)	10 (46%)
High	174	135 (78%)	126 (93%)	39 (22%)	7 (18%)

It is difficult for any diagnostic test to contribute information when the pretest probability of disease is extremely low or extremely high. As the pretest likelihood gets higher and higher, a positive test result provides a smaller and smaller increment of information, while a negative test result is more and more likely to be a false negative. Conversely, as the pretest likelihood of disease approaches zero, positive test results are more and more likely to be false positives. These considerations are of course applicable to all diagnostic tests, not just to the GenESA System.

To interpret the data another way, one can estimate the post-test likelihood of CAD, given the pre-test likelihood and the result of a GenESA System test (Diamond GA, et al., NEJM 1979: 300;1350-58). These results are shown in Table 4 for perfusion imaging and confirm the general discussion of the previous paragraph.

Table 4
Post-Test Likelihood of Coronary Artery Disease Given the Pre-Test Likelihood and the Result of GenESA System Testing Assessed with Radionuclide Imaging

Pre-Test Likelihood	Post-Test Likelihood	
	with positive GenESA test	with negative GenESA test
10%	16	4
20%	30	9
30%	43	15
40%	54	22
50%	64	29
60%	72	38
70%	80	49
80%	87	62
90%	94	79

3. Echocardiography: Sensitivity/Specificity

The ability of GenESA System echocardiography tests to predict the results of coronary angiography was assessed in two studies, involving a total of 389 patients. Patients were selected as in the radionuclide studies. The blinded re-reading of the results from the lower-risk study was technically inadequate, and the results shown in Table 5 for that study are based on non-blinded readings.

Table 5
Sensitivity, Specificity and Predictive Fractions for Echocardiography with the GenESA System

Study	Sensitivity	Specificity	Positive Predictive Fraction	Negative Predictive Fraction
High Risk	110/131 (84%)	4/16 (25%)	110/122 (90%)	4/25 (16%)
Lower Risk	137/194 (71%)	32/48 (67%)	137/153 (90%)	32/89 (36%)

4. Echocardiography: Predictive Value of the GenESA System Test

The 381 patients with demographic data available who underwent coronary angiography and GenESA System testing assessed with echocardiography were categorized as was done for perfusion imaging and the characteristics of the three groups are summarized in Table 6 below.

Table 6
Characteristics of 381 Patients Who Each Underwent Coronary Angiography and had a GenESA System Test Assessed with Echocardiography

Pretest CAD likelihood Group called % (N) of Patients	<20% "Low" 3% (13)	20-80% "Intermediate" 57% (103)	>80% "High" 70% (265)
Age 65 years	8% (1)	23% (24)	38% (101)
Male	15% (2)	53% (56)	89% (235)
Typical Angina	0% (0)	18% (19)	79% (210)
Atypical Angina	62% (8)	51% (53)	15% (40)
Hyperlipidemia	46% (6)	57% (60)	62% (165)
Diabetes	0% (0)	16% (17)	20% (53)
Smoking	23% (3)	31% (33)	38% (101)
Prior MI	0% (0)	15% (16)	53% (140)
MI on ECG	0% (0)	0% (0)	28% (73)
ST-T Abnormality	23% (3)	21% (22)	37% (99)
# Patients with:			
1 Risk Factor	31% (4)	5% (5)	0% (0)
2 Risk Factors	62% (8)	31% (32)	2% (5)
3 Risk Factors	8% (1)	40% (41)	22% (58)
4 Risk Factors	0% (0)	22% (23)	26% (71)
≥5 Risk Factors	0% (0)	2% (2)	49% (131)
Mean (±SD) # Risk Factors/Patient	1.8±0.6	2.9±0.9	4.6±1.3
Angiography positive	39% (5)	55% (57)	78% (207)

As with perfusion imaging and summarized in Table 7 below, the performance of the GenESA System varied from one subgroup to another; it was most uniformly accurate in patients with an intermediate pre-test likelihood of disease.

Table 7
Predictive Value of GenESA System Testing when used with Echocardiography

Pretest probability of positive angiogram	N	Positive GenESA Test	Positive GenESA test was correct (angiogram positive)	Negative GenESA Test	Negative GenESA test was correct (angiogram negative)
Low	13	5 (38%)	2 (40%)	8 (62%)	7 (88%)
Intermediate	103	57 (55%)	47 (83%)	46 (45%)	21 (46%)
High	265	207 (78%)	193 (93%)	58 (22%)	7 (12%)

It is difficult for any diagnostic test to contribute information when the pretest probability of disease is extremely low or extremely high (see earlier discussion of perfusion imaging results). As for perfusion imaging, the post-test likelihood of CAD, given the pre-test likelihood and the result of a GenESA System test, was estimated. These results are shown in Table 8 and confirm the general discussion of the previous paragraph.

Table 8
Post-Test Likelihood of Coronary Artery Disease Given the Pre-Test Likelihood and the Result of GenESA System Testing Assessed with Echocardiography

Pre-Test Likelihood	Post-Test Likelihood	
	with positive GenESA test	with negative GenESA test
10%	16	5
20%	30	10
30%	43	15
40%	54	22
50%	63	30
60%	72	39
70%	80	50
80%	87	63
90%	94	79

INDICATIONS AND USAGE

The GenESA System delivers arbutamine, a catecholamine, through a closed-loop, computer-controlled drug-delivery system to elicit acute cardiovascular responses similar to those produced by exercise. In patients with suspected coronary artery disease (CAD) who cannot exercise adequately, stress induction with the GenESA System is indicated as an aid in diagnosing the presence or absence of CAD.

The effectiveness of the GenESA System has been demonstrated in clinical studies using radionuclide myocardial perfusion imaging to predict the results of coronary angiography. These studies were in patients with high and lower risks of CAD and utilized blinded, central reading of images. Estimates of sensitivity, specificity and predictive values are presented in the "Clinical Trials" section.

Although the effectiveness of the GenESA System was also assessed in similar clinical studies utilizing echocardiography to predict the results of coronary angiography, the blinded, central reading of the images from the lower-risk echocardiography study was technically inadequate. Estimates of sensitivity, specificity and predictive values, based on the non-blinded readings of echocardiograms at the local study sites, are presented for the lower-risk patients (see Clinical Trials). For the study of high-risk patients, the estimates are based on valid, blinded, central reading of images.

Like exercise testing, cardiac stress testing with the GenESA System must always be performed under the direct supervision of a physician, and cardiac emergency equipment and supplies (defibrillator, intravenous β-blocker, etc.) must always be available. Arbutamine must not be administered without use of the GenESA Device.

CONTRAINDICATIONS

Arbutamine is contraindicated in patients with idiopathic hypertrophic subaortic stenosis, in patients with a history of recurrent sustained ventricular tachycardia, in patients with congestive heart failure (NYHA Class III or IV), and in patients who have shown previous manifestations of hypersensitivity to arbutamine. The GenESA System must not be used in the presence of an implanted cardiac pacemaker or automated cardioverter/defibrillator.

WARNINGS

During clinical trials that included 2082 patients with known or suspected coronary artery disease, arbutamine administration was associated with 10 serious adverse events, including 3 episodes of ventricular fibrillation, 1 episode of sustained ventricular tachycardia, 3 episodes of atrial fibrillation (see Table 10 for a summary of all arrhythmias reported as adverse events), 1 myocardial infarction and 2 cases of severe angina. Two of the three cases of ventricular fibrilation occurred after the GenESA Device had detected a plateau in HR response and had terminated arbutamine infusion, but the physician restarted the infusion. There were no deaths.

The incidence of serious adverse events is thus low, less than 0.5%. Nevertheless, the potential information to be gained through the use of arbutamine, delivered using the GenESA Device (see INDICATIONS AND USAGE), must be weighed against the potential risks to each patient.

Arbutamine may precipitate or exacerbate supraventricular and ventricular arrhythmias and its administration is not recommended in patients with a history of sustained arrhythmias of this nature. Given the proarrhythmic effects of certain antiarrhythmic drugs, particularly Class 1 agents such as quinidine, lidocaine and flecainide, arbutamine should not be administered to patients receiving such therapy.

Supraventricular or ventricular arrhythmias can occur during the administration of arbutamine (see ADVERSE REACTIONS) with isolated premature ventricular and atrial contractions being the most frequent arrhythmias. Most arrhythmias were self-limiting and all resolved without sequelae. If any arrhythmias are of clinical concern, drug infusion should be discontinued immediately and appropriate therapy (e.g. intravenous β-blockers - see OVERDOSAGE) administered, if necessary. The GenESA Device is not designed to detect arrhythmias. Appropriate monitoring equipment, such as a diagnostic quality ECG machine, must therefore be used during a GenESA System test. The GenESA Device administers arbutamine based upon HR response and it is possible that, in the presence of an arrhythmia, the GenESA Device may register an inaccurate HR. The ECG should be monitored carefully and appropriate action, including, if necessary, discontinuation of drug infusion, taken in the event of inaccurate HR detection.

Arbutamine may cause rapid increases or paradoxical decreases in HR and systolic blood pressure. Discontinuation of arbutamine infusion results in reversal of these effects. The infusion may be restarted, if considered clinically appropriate (see DOSAGE AND ADMINISTRATION).

The safety of arbutamine administration in patients with recent (within 30 days) myocardial infarction has not been formally evaluated. The administration of arbutamine is not recommended in patients with unstable angina, mechanical left ventricular outflow obstruction such as severe valvular aortic stenosis, uncontrolled systemic hypertension, a cardiac transplant, a history of cerebrovascular accident or peripheral vascular disorder resulting in cerebral or aortic aneurysm. In addition, arbutamine is not recommended in patients with narrow-angle glaucoma or uncontrolled hyperthyroidism.

Arbutamine should not be administered to patients receiving digoxin, atropine (or other anticholinergic drugs) or tricyclic antidepressants. As the dosing of arbutamine is based on the HR response of the patient, the use of atropine to enhance the chronotropic response to arbutamine is not recommended.

Reactions suggestive of hypersensitivity have been reported occasionally with the administration of other catecholamines [such as Dobutrex® (dobutamine)]. Like other parenterally administered catecholamines, GenESA contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than nonasthmatic individuals. No such reactions have been reported with arbutamine.

PRECAUTIONS-(See WARNINGS)

During the administration of arbutamine, as with any parenteral catecholamine, ECG and blood pressure should be continuously monitored. The GenESA Device provides such monitoring capabilities but a diagnostic-quality ECG machine must also be used to monitor the ECG.

Like other catecholamines, arbutamine can produce a transient reduction in serum potassium concentration, rarely to hypokalemic levels. In one study, the transient decrease in serum potassium after arbutamine was greater in patients with arrhythmias (N=168), than to those without arrhythmias (N=72).

Overall, changes in serum potassium in patients with clinically significant arrhythmias were not clearly different from those seen in other patients.

As seen with other catecholamines, GenESA infusion is associated with a transient increase in corrected QT interval, as measured from the surface ECG. This effect did not appear to be associated with an increased incidence of arrhythmias.

The acute use of the GenESA System for diagnostic testing makes it unlikely that alterations in renal and /or hepatic function will influence the safety and diagnostic efficacy of a GenESA System test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Arbutamine is intended for single-dose use only and therefore animal carcinogenicity or long-term toxicity studies have not been performed.

Arbutamine was shown to be non-genotoxic in the Ames bacterial reverse mutation assay, with and without S9 mix, and in the mouse micronucleus test. Arbutamine was positive in the human lymphocyte chromosomal aberration assay (>66 μg/mL) and in the mouse lymphoma cell assay (>39 μg/mL).

Studies to determine the effect of arbutamine on the impairment of fertility have not been performed.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies performed in rats and in rabbits at doses up to 0.9 and 0.36 mg/kg/day I.V., respectively (4 and 12 times the maximum recommended human dose on a mg/m² basis), revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, arbutamine should be used during pregnancy only if clearly needed.

Drug Interactions

Beta-adrenergic antagonists may attenuate the response to arbutamine and should be withdrawn, as recommended in the relevant product labeling, at least 48 hours before conducting a GenESA System test. There was no evidence of drug-drug interactions in clinical studies in which arbutamine was administered concurrently with other drugs, including platelet aggregation inhibitors, nitrates, and calcium channel blockers.

ADVERSE REACTIONS

Adverse events were recorded during controlled clinical trials in 2082 patients with known or suspected coronary artery disease. Serious adverse events (ventricular and atrial fibrillation, and severe cardiac ischemia) are described above (see WARNINGS).

The most frequently reported adverse events in the 2082 patients were: tremor (15%), angina pectoris (12%), non-serious cardiac arrhythmias (12%), headache (9%), and hypotension (6%). Adverse events occurring in ≥ 1% of the 2082 patients are shown in Table 9:

Table 9
Incidence of Most Frequent (≥ 1%) Adverse Events with Arbutamine

	Incidence (%) of Adverse Events
Tremor	15
Angina pectoris	12
Cardiac arrhythmias	12
Ventricular	6
Supraventricular	4
Headache	9
Hypotension	6
Chest pain	4
Dizziness	4
Dyspnea	4
Palpitation	4
Flushing	3
Hot flushes	3
Nausea	3
Paresthesia	2
Anxiety	1.9
Pain (non-specific)	1.8
Increased sweating	1.5
Fatigue	1.3
Taste perversion	1.3
Dry mouth	1.1
Hypoesthesia	1.0
Vasodilation	1.0

Other adverse events, considered at least possibly related to arbutamine administration and occurring in <1% of the 2082 patients, and seen at least twice, are listed by body system.

- Cardiovascular: myocardial ischemia (0.1%) - see WARNINGS. ST segment depression (0.6%), hypertension (0.4%).
- Body as a Whole: asthenia (0.4%), malaise (0.2%), rigors (0.2%), back pain (0.1%).
- Central and Peripheral Nervous System Disorders: twitching (0.3%).
- Gastrointestinal System: abdominal pain (0.1%).
- Psychiatric Disorders: nervousness (0.7%), agitation (0.2%).
- Respiratory System Disorders: coughing (0.2%), bronchospasm (0.1%).
- Other: rash (0.2%), abnormal lacrimation (0.1%), application site reaction (0.1%).

Cardiac arrhythmias were reported as adverse events, if symptomatic or considered clinically significant, by the physician supervising the stress test. Overall cardiac arrhythmias, as identified by the investigator as adverse events, are shown in Table 10:

Table 10
Incidence of Arrhythmias Reported as Adverse Events

	Incidence of Arrhythmias Reported as Adverse Events (N=2082)
Total number of patients	251 (12%)
Ventricular	130 (6.2%)
Ventricular fibrillation	3 (0.1%)
Ventricular tachycardia	37 (1.8%)
Other ventricular*	106 (5.1%)
Supraventricular	79 (3.8%)
Supraventricular tachycardia	39 (1.9%)
Atrial fibrillation	20 (1.0%)
Other supraventricular**	24 (1.2%)
Junctional	16 (0.8%)
Bradycardia	23 (1.1%)
Sinus tachycardia	18 (0.9%)
Heart Block†	3 (0.1%)
Sinus arrhythmia	1 (0.05%)

* Includes premature ventricular contractions (PVCs), couplets, triplets (rate ≤ 100 bpm), multifocal PVCs, ventricular bigeminy/trigeminy and idioventricular rhythm

** Includes premature atrial contractions and atrial arrhythmia (coronary sinus rhythm)

† Includes sinoatrial block and right bundle branch block

NOTE: Patients may have experienced more than one arrhythmia

OVERDOSAGE - (See WARNINGS)

Because arbutamine delivery is controlled by the GenESA Device to give a defined increase in heart rate, overdosage is unlikely to occur. The maximum total dose permitted by the GenESA Device is 10 μg/kg. If overdosage occurs it should be short-lived, as arbutamine is metabolized rapidly, and most effects would be extensions of arbutamine's pharmacologic effects.

The symptoms of toxicity are those of catecholamine excess: tremor, headache, flushing, hypotension, dizziness, paresthesia, nausea, hot flushes, angina, increased sweating and anxiety. The positive chronotropic and inotropic effects of arbutamine on the myocardium may cause tachyarrhythmias, hypertension, myocardial infarction and ventricular fibrillation. If arbutamine is ingested, unpredictable absorption may occur from the mouth and gastrointestinal tract.

Treatment - initial actions include discontinuing administration, establishing an airway and ensuring adequate oxygenation and ventilation. Severe signs or symptoms (angina, tachyarrhythmias, ST segment abnormalities, hypotension) may be successfully treated with an intravenous β-blocker, such as metoprolol, esmolol or propranolol, at I.V. doses of 7.5-50 mg, 10-80 mg and 0.5-2 mg, respectively. Other treatment, such as sublingual nitrates, should be used if considered clinically appropriate. Given the rapid elimination of arbutamine, forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion are unlikely to be required for arbutamine overdosage.

DOSAGE AND ADMINISTRATION

Before using the GenESA System, it is essential to read and understand The GenESA System Directions For Use in addition to this section of labeling. The GenESA System Directions for Use describe the complete operating instructions for the GenESA Device and the delivery of arbutamine.

GenESA (arbutamine hydrochloride, sterile solution for infusion, 0.05 mg/mL) must be administered from the prefilled syringe and must not be diluted or transferred to another syringe. GenESA is intended for direct intravenous infusion ONLY with the GenESA Device.

The GenESA Device comprises a single channel ECG (R wave) detector, a non-invasive blood pressure monitor, computer software (closed-loop algorithm) which controls drug delivery, an intravenous syringe pump, display functions and an operator key pad. The GenESA Device individualizes the dosing regimen of arbutamine according to the HR response of the patient using the closed-loop algorithm. The physician selects the desired rate of HR rise (HR SLOPE: either LOW, 4 bpm/min; MEDIUM, 8 bpm/min; or HIGH, 12 bpm/min); alternatively any value from 4-12 bpm/min may be selected and the maximum HR to be achieved (HR TARGET - estimated by the device as (220-age) 85%, or adjusted manually by the operator) for each patient test. The choice of HR Slope should be based upon the desired duration of the test and the rate of HR rise, judged by the physician, to be most appropriate. Clinical data, obtained using a HR Slope of 8 bpm/min, support the use of this MEDIUM slope in a majority of patients.

Upon starting the test, the GenESA Device administers a small dose of arbutamine (0.1 μg/kg/min for 1 minute) and measures the patient's HR response. The device then calculates the difference between the desired and actual HR response, and maintains or modifies, as necessary, the infusion rate. The maximum infusion rate delivered by the GenESA Device is 0.8 μg/kg/min and the maximum total dose is 10 μg/kg. The GenESA Device includes a "HOLD HR" feature that, when activated, allows HR to be maintained at approximately that level for up to 5 minutes.

Monitoring features of the GenESA Device include continuous display of ECG, HR, blood pressure and dosing information. In addition, the device has a series of "alerts" that warn of conditions that may require attention and "alarms" that stop drug delivery due to a potential safety hazard. Each alert or alarm provides a visual message and an audible tone to warn the operator. The physician conducting the GenESA System test may manually interrupt the delivery of arbutamine at any time, if clinically appropriate. The infusion of arbutamine may be restarted by the operator if the condition resulting in the interruption of infusion has been corrected, a diagnostic endpoint has not been reached, and it is considered safe and appropriate to do so.

"Heart rate saturation" (a flattening or plateau of the HR response to increasing dose of arbutamine) describes the maximal HR response to arbutamine and is an endpoint of the GenESA System test. If such a flattening or plateau of the HR response is detected when the HR is ≤ 40 bpm above the baseline level, restart of the arbutamine infusion is allowed. If the HR is >40 bpm above baseline and a HR saturation alarm occurs, restart of the arbutamine infusion is prevented by the GenESA Device [since it is unlikely that any further clinically significant increase in HR will occur following restart and there is a potential risk of serious cardiac arrhythmias (see **WARNINGS**)].

The infusion of arbutamine should be terminated when a diagnostic endpoint (e.g. ST segment deviation on ECG) has been reached, if clinically significant symptoms or arrhythmias occur, or if clinically appropriate for any other reason. The GenESA Device will stop drug delivery when the maximum HR limit (HR TARGET) has been reached or after a total of 10 μg/kg arbutamine has been delivered. Following completion of the infusion, the patient should be monitored (using the GenESA Device or other means) until HR and blood pressure have returned to acceptable levels.

For Basic Operating Instructions and other essential information on the use of the GenESA System, see the Quick Reference pull-out cards attached to the GenESA Device.

SYRINGE AND PLUNGER ROD ASSEMBLY:

- Remove the prefilled glass syringe and plunger rod from the package.
- Inspect the grey tip cap and stopper for proper engagement. Evidence of leakage or a loose tip cap may indicate a violation of sterility.

  Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
- Thread the plunger rod into the stopper clockwise until fully seated (approximately one full revolution).
- Hold the syringe vertically (tip UP), remove the tip cap, and manually express any air from the syringe.
- Attach the IV administration set to the syringe luer lock. Use a push and twist (clockwise) action until fully engaged.
- Load the assembled syringe/IV set into the GenESA Device as instructed in The GenESA System Directions For Use.

HOW SUPPLIED

GenESA (arbutamine hydrochloride, sterile solution for infusion, 0.05 mg/mL), is available as a 20 mL prefilled syringe. Each syringe contains 1 mg of arbutamine hydrochloride. Store at 2-8°C. Protect from light. (NDC 0703-1105-01).

CAUTION: Federal (USA) law prohibits dispensing without a prescription.

Gensia Automedics, Inc.
San Diego, California, 92121
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GENSIA AUTOMEDICS™